EXHIBIT X

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Supplement to the 2019 Integrated Science Assessment for Particulate Matter

Office of Research and Development
Center for Public Health & Environmental Assessment, Research Triangle Park, NC

EPA United States
Environmental Protection
Agency

Supplement to the 2019 Integrated Science Assessment for Particulate Matter

May 2022

Center for Public Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC

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CONTENTS

LIST OF TABLES

LIST OF FIGURES

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ACRONYMS AND ABBREVIATIONS

Acronym/ Abbreviation	Meaning
AARP	American Association of Retired Persons
ABI	ankle-brachial index
ACS	American Cancer Society
adj	adjustment
AF	atrial fibrillation
Ag Health	Agricultural Health Study
AHSMOG	Adventist Health Study and Smog
AIC	Akaike information criterion
AL	Alabama
AMI	acute myocardial infarction
AN	ammonium nitrate
AOD	aerosol optical depth
APPROACH	Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease
AQCD	Air Quality Criteria Document
AQS	Air Quality System
AS	ammonium sulfate
ASD	autism spectrum disorder
avg	average
BAD	bronchial artery diameter
BASIC	Brain Attack Surveillance in Corpus Christi
BC	black carbon
b_{ext}	light extinction coefficient
BME	Bayesian maximum entropy
BMI	body mass index
BP	blood pressure
BRFSS	Behavioral Risk Factor Surveillance System
CA	California
CAC	coronary artery calcification
CAD	coronary artery disease
Cancer Prev	cancer prevention

Acronym/ Abbreviation	Meaning
CanCHEC	Canadian Census Health and Environment Cohort
CAN-Marg	Canadian Marginalization Index
CAPs	concentrated ambient particles
CASAC	Clean Air Scientific Advisory Committee
CATHGEN	Catheterization Genetics study
CBSA	core-based statistical area
CBVD	cerebrovascular disease
CCHEC	Canadian Census Health and Environment Cohort
CCHS	Canadian Community Health Survey
CFR	case fatality rate
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
cIMT	carotid intima-media thickness
CM	coarse mass
CMA	census metropolitan area size
CMAQ	Community Multiscale Air Quality model
CMR	cardiovascular mortality rate
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
C-R	concentration-response
CSN	Chemical Speciation Network
CTM	chemical transport model
CTS	California Teachers Study
C-V	cross-validation
CVD	cardiovascular disease
DBP	diastolic blood pressure
DC	District of Columbia
DE	diesel exhaust
df	degrees of freedom

Acronym/ Abbreviation	Meaning
DID	difference-in-difference
DNA	deoxyribonucleic acid
DOW	day of week
DRAM	doubly robust additive model
DVT	deep vein thrombosis
EC	elemental carbon
ECG	electrocardiogram
ED	emergency department
EFFECT	Enhanced Feedback for Effective Cardiac Treatment
EJ	environmental justice
EPA	Environmental Protection Agency
ESCAPE	European Study of Cohorts for Air Pollution Effects
ESRD	end-stage renal disease
exp	exposure
FA	filtered air; fatty acid
FD	find dust
FEV$_1$	forced expiratory volume in 1 second
FMD	flow-mediated dilation
FVC	forced vital capacity
GA	Georgia
GAM	generalized additive model
GLM	generalized linear model
GEOS-Chem	Goddard Earth Observing System-Chem
GP	general practitioner
GPS	generalized propensity score
GWR	geographically weighted regression
h	hour(s)
HA	hospital admission
HDL-c	High-density lipoprotein cholesterol
Health Prof	health professionals
HeartSCORE	Heart Strategies Concentration on Risk Evaluation
HEI	Health Effects Institute

Acronym/ Abbreviation	Meaning
HEPA	high efficiency particle filter
HF	heart failure; high frequency
HHD	hypertensive heart disease
HISA	Highly Influential Scientific Assessment
HNR	Heinz Nixdorf Recall (study)
HPFU	Health Professionals Follow-Up Study
HR	hazard ratio
HRV	heart rate variability
HS	hemorrhagic stroke
HSC	Harvard Six Cities
HYSLPLIT	HYbrid Single-Particle Lagrangian Integrated Trajectory
IAD	inter-adventitial diameter
ICD-10	International Classification of Disease version 10
ICD-9	International Classification of Disease version 9
ICU	intensive care unit
IDW	inverse distance weighting
IHD	ischemic heart disease
IL	Illinois
IMPROVE	Interagency Monitoring of Protected Visual Environments
InMAP	Intervention Model for Air Pollution
IPTW	inverse probability of treatment weighting
IPW	inverse probability weighting
IQR	interquartile range
IRD	Index of Racial Dissimilarity
IRP	Integrated Review Plan
IRR	incidence rate ratio
IS	ischemic stroke
IV	instrumental variable
JHS	Jackson Heart Study
km	kilometer(s)
km2	square kilometer(s)
LDH	lactate dehydrogenase

Acronym/ Abbreviation	Meaning
LDL-c	low-density lipoprotein cholesterol
LF	low frequency
LUR	land use regression
LUR-BME	land use regression—Bayesian maximum entropy
LV	left ventricular
m^2	Square meter(s)
MAP	mean arterial pressure
MAPLE	mortality-air pollution associations in low-exposure environments
max	maximum
MCAPS	Medicare Cohort Air Pollution Study
MCC	Multi-City Multi-Country Collaborative Research Network
mCCHS	Canadian Community Health Survey—mortality cohort
MCM	multi-cause multicity
MD	Maryland
MESA	Multi-Ethnic Study of Atherosclerosis
mg	milligram(s)
MI	myocardial infarction
min	minimum
MINAP	Myocardial Ischemia National Audit Project
MISR	Multiangle Imaging Spectroradiometer
MISS	monotonically increasing smoothing splines
mm Hg	millimeters of mercury
mo	month(s)
MO	Missouri; month
MR	mortality ratio
MRR	mortality risk ratio
NAAQS	National Ambient Air Quality Standards
NAPS	National Air Pollution Surveillance System
NC	number concentration; North Carolina

Acronym/ Abbreviation	Meaning
NCHS	National Center for Health Statistics
NEI	National Emissions Inventory
NH	non-Hispanic
NHIS	National Health Interview Survey
NHS	Nurses' Health Study
NIH	National Institutes of Health
NIH-AARP	National Institutes of Health–American Association of Retired Persons (diet and health cohort)
NMMAPS	National Morbidity, Mortality, and Air Pollution Study
NN	Normal-to-Normal
NO_2	nitrogen dioxide
NO_3	nitrate
NO_X	oxides of nitrogen ($NO + NO_2$)
NPMs	neighborhood PM monitors
NR	not reported
NSTEMI	non-ST segment elevation MI
O_3	ozone
OC	organic carbon
OHCA	out-of-hospital cardiac arrest
OLS	ordinary least squares
OM	organic matter
OMB	Office of Management and Budget
ONPHEC	Ontario Population Health and Environment Cohort
OR	odds of recurrent
Ox	Redox weighted average of NO_2 and O_2
PA	Pennsylvania
PAH	polycyclic aromatic hydrocarbon(s)
PE	prediction error
PEF	peak expiratory flow
PM	particulate matter

Acronym/ Abbreviation	Meaning
PM_{10}	particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 um
$PM_{10-2.5}$	particulate matter with a nominal mean aerodynamic diameter greater than 2.5 um and less than or equal to 10 um
$PM_{2.5}$	particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 um
POM	particulate organic matter
ppb	parts per billion
ppm	parts per million
PQAPP	Program-level Quality Assurance Project Plan
PREMIER	Prospective Registry Evaluating Myocardial Infraction: Events and Recovery
QA	quality assurance
QAPP	quality assurance project plans
QRS	time interval between the beginning of the Q wave and the peak of the S wave
r	correlation coefficient
R^2	coefficient of determination
RAMP	Real-time Affordable Multi-Pollutant
RC	regression calibration
RCS	restricted cubic splines
redox	reduction-oxidation
REGARDS	REasons for Geographic and Racial Differences in Stroke
re-HA	Readmission to the hospital
RF	radiative forcing
RH	relative humidity
RMSS	root mean square standardized
RR	relative risks
RRS	racial residential segregation
RV	right ventricular
SARS	severe acute respiratory syndrome

Acronym/ Abbreviation	Meaning
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SC	surface area concentration
SCHIF	Shape Constrained Health Impact Function
SD	standard deviation
SDI	social deprivation index
SDNN	standard deviation of NN
SE	standard error
SED	socioeconomic deprivation
SEIR	susceptible-exposed-infected-recovered
SES	socioeconomic status
SHS	second-hand smoke
SHV	Social and Health Vulnerability
sICAM	soluble intercellular adhesion molecule 1
SO_2	sulfur dioxide
SO_4	sulfate
SPARCS	New York State Department of Health Statewide Planning and Research Cooperative System
SPE	standardized prediction error
ST	beginning of S wave to end of T wave
STEMI	ST elevated myocardial infarction
sVCAM	Soluble vascular cell adhesion molecule 1
SHV	Social Health Vulnerability
SWAN	Study of Women's Health Across the Nation
TRAP	traffic-related air pollution
TrIPS	Trucking Industry Particle Study
TRIUMPH	Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction
TX	Texas

Acronym/ Abbreviation	Meaning
UFIREG	Ultrafine Particles—An Evidence-Based Contribution to the Development of Regional and European Environmental and Health Policy
UFP	ultrafine particle
U.S.	United States of America
U.S. EPA	U.S. Environmental Protection Agency
USRDS	U.S. Renal Data System
W	west
WHI	Women's Health Initiative
WHO	World Health Organization
WS Fe	water-soluble iron
yr	year(s)
ZIP	Zone Improvement Plan

EXECUTIVE SUMMARY

In June 2021, the U.S. Environmental Protection Agency (EPA) announced it will reconsider the December 2020 decision to retain the particulate matter (PM) National Ambient Air Quality Standards (NAAQS). As part of the reconsideration process, EPA indicated that it would develop a supplement to the 2019 Integrated Science Assessment for PM (2019 PM ISA) to thoroughly evaluate the most up-to-date science that became available after the literature cutoff date of the 2019 PM ISA that could either further inform the adequacy of the current PM NAAQS or address key scientific topics that have evolved since the 2020 PM NAAQS review was completed.

Within this Supplement, EPA presents an evaluation of recent studies (i.e., published since the literature cutoff date of the 2019 PM ISA) that potentially are of greatest relevance to the reconsideration of the PM NAAQS in the context of the findings of the 2019 PM ISA. The studies that formed the basis of the evaluation consist of U.S. and Canadian studies, specifically: (a) epidemiologic studies for health effect categories for which the 2019 PM ISA concluded a *causal relationship* (i.e., short- and long-term $PM_{2.5}$ exposure[1] and cardiovascular effects and mortality); (b) epidemiologic studies that employed statistical approaches that attempt to more extensively account for confounders and are more robust to model misspecification (i.e., used alternative methods for confounder control)[2] or conducted accountability analyses; (c) studies that address key scientific topics that have evolved since the literature cutoff date for the 2019 PM ISA, including experimental studies conducted at near-ambient $PM_{2.5}$ concentrations, epidemiologic studies that examined the association between $PM_{2.5}$ exposure and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and coronavirus disease 2019 (COVID-19) death, and epidemiologic or exposure studies that examined disparities in $PM_{2.5}$ exposure or health risks by race and ethnicity or socioeconomic status; and (d) studies that examined public preferences for visibility impairment and/or developed methodologies or conducted quantitative analyses of light extinction. This Supplement to the 2019 PM ISA does not represent a full multidisciplinary evaluation of evidence that results in the formation of weight-of-evidence conclusions (i.e., causality determinations), but instead puts the results of recent studies that encompass specific criteria in the context of the scientific conclusions presented within the 2019 PM ISA. As such, the Supplement indicates whether recent evidence supports (is consistent with), supports and extends (is consistent with

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[1] Consistent with the scope of the 2019 PM ISA (Section P.3.1), short-term exposures are defined as those exposures occurring over hours up to 1 month, while long-term exposures are defined as those exposures occurring over 1 month to years.

[2] In the peer-reviewed literature, these epidemiologic studies are often referred to as causal inference studies or studies that used causal modeling methods. For the purposes of this Supplement this terminology is not used to prevent confusion with the main scientific conclusions (i.e., the causality determinations) presented within an ISA. In addition, as is consistent with the weight-of-evidence framework used within ISAs and discussed in the Preamble to the Integrated Science Assessments, an individual study on its own cannot provide the evidence needed to make a causality determination, but instead represents a piece of the overall body of evidence.

and reduces uncertainties), or does not support (is not consistent with) the causality determinations detailed in the 2019 PM ISA for the health effects categories evaluated within this Supplement.

This Supplement to the 2019 PM ISA finds that recent studies further support, and in some instances extend, the evidence that formed the basis of the causality determinations presented within the 2019 PM ISA that characterizes relationships between PM exposure and health (i.e., cardiovascular effects and mortality) and welfare effects (i.e., visibility impairment). In brief, this Supplement finds the following:

- Recent U.S. and Canadian epidemiologic studies examining short- and long-term $PM_{2.5}$ exposure and cardiovascular effects and mortality provide evidence that further supports, and in some instances extends, the evidence that contributed to the conclusion of a *causal relationship* detailed in the 2019 PM ISA. Relative to the studies evaluated in the 2019 PM ISA, many of the studies report positive associations at lower $PM_{2.5}$ concentrations (i.e., annual $PM_{2.5}$ concentrations ranging from 5.9 to 16.5 micrograms per cubic meter ($\mu g/m^3$); mean 24-hour avg $PM_{2.5}$ concentrations ranging from 7.1 to 15.4 $\mu g/m^3$).

  - Recent U.S. and Canadian epidemiologic studies examining short- and long-term $PM_{2.5}$ exposure and cardiovascular effects provide evidence that is consistent with the studies evaluated in the 2019 PM ISA. Studies examining short-term $PM_{2.5}$ exposure report consistent positive associations for cardiovascular-related emergency department (ED) visits and hospital admissions, specifically for ischemic heart disease (IHD), myocardial infarction (MI), and heart failure (HF). For long-term exposure, strong evidence remains for cardiovascular-related mortality with support from studies of cardiovascular morbidity outcomes including coronary heart disease (CHD), stroke, and atherosclerosis progression, among individuals with preexisting diseases or patients followed after a cardiac event or procedure. Associations persisted across studies conducted in different geographic locations, populations with diverse demographic characteristics, and study designs (i.e., different exposure assessment methods, and confounder control).

  - Relatively few recent U.S. and Canadian epidemiologic studies examined short-term $PM_{2.5}$ exposure and mortality; however, these studies continue to provide evidence of positive associations with both all-cause and total (nonaccidental) mortality as well as with cause-specific mortality outcomes.

  - A number of recent long-term $PM_{2.5}$ exposure and mortality studies conducted in cohorts consisting of populations with diverse demographic characteristics and encompassing large geographic areas report consistent, positive associations, with most reporting mean annual $PM_{2.5}$ concentrations ranging from 5.9 to 11.65 $\mu g/m^3$.

    - Across epidemiologic studies examining both cardiovascular effects and mortality, sensitivity analyses as well as individual studies further inform uncertainties in the evidence base (i.e., copollutant confounding, control for confounders such as temporal trends and temperature, and the concentration-response [C-R] relationship). Such analyses increase confidence in the relationship for both short- and long-term $PM_{2.5}$ exposures and both health effect categories, and further support the causality determinations presented in the 2019 PM ISA.

    - Since the completion of the 2019 PM ISA, numerous U.S. and Canadian epidemiologic studies conducted accountability analyses or employed statistical approaches that attempt to account more extensively for confounders and are

more robust to model misspecification (i.e., used alternative methods for confounder control) to examine both short- and long-term $PM_{2.5}$ exposure and cardiovascular effects and mortality. These studies, which used a variety of statistical methods to control for confounding bias, consistently report positive associations, which further supports the broader body of epidemiologic evidence for both cardiovascular effects and mortality.

- o   Several recent U.S. and Canadian studies provide additional insight on the health effects of $PM_{2.5}$, including a recent controlled human exposure study conducted at near-ambient concentrations, which provided initial evidence of both lung and cardiac function changes in young, healthy participants.

- o   In response to the global COVID-19 pandemic, numerous studies provide initial assessments of short- and long-term $PM_{2.5}$ exposure and SARS-CoV-2 infection and COVID-19 death. While some of these studies report initial evidence of positive associations, these studies are subject to methodological limitations and require additional exploration.

- o   The 2019 PM ISA provided evidence that specific lifestages and populations are at increased risk of a $PM_{2.5}$-related health effect. Recent U.S. and Canadian epidemiologic studies support and expand the evidence base within the 2019 PM ISA and indicate that there are both $PM_{2.5}$ exposure and health risk disparities by race and ethnicity among minority populations, specifically Black populations. Additionally recent evidence supports the evidence presented in the 2019 PM ISA that there may be $PM_{2.5}$ exposure and health risk disparities by socioeconomic status (SES), specifically among people of low SES.

- •   Recent studies continue to support a relationship between PM and visibility impairment and provide additional insights on the impact of choice of metric on preference study results, impacts of changing PM composition on the relationship between PM and visibility impairment, and alternative approaches to estimating light extinction.

1. INTRODUCTION AND SCOPE

1.1. Introduction

The U.S. Environmental Protection Agency (EPA) completed the Integrated Science Assessment for Particulate Matter (PM ISA) in December 2019 (hereafter referred to as the 2019 PM ISA) (U.S. EPA, 2019). The 2019 PM ISA builds upon the evidence evaluated and scientific conclusions presented in prior assessments, including the 2009 PM ISA (U.S. EPA, 2009) and earlier assessments, e.g., 2004 PM Air Quality Criteria Document [AQCD; (U.S. EPA, 2004)] and 1996 PM AQCD (U.S. EPA, 1996). Within the 2019 PM ISA, evidence spanning scientific disciplines (e.g., atmospheric chemistry, exposure science, animal toxicological, human clinical, epidemiology) was evaluated to assess the causal nature of relationships between short- and long-term[3] PM exposure and health and PM and nonecological welfare effects using a weight-of-evidence approach extensively detailed in the *Preamble to the Integrated Science Assessments* (U.S. EPA, 2015) and the Appendix of the 2019 PM ISA.[4]

The key science judgments (i.e., causality determinations) detailed within the 2019 PM ISA directly informed the development of conclusions outlined within the *Policy Assessment for the Review of the PM NAAQS* (2020 PM PA) (U.S. EPA, 2020b). These key science judgments formed the basis of the discussion on potential alternative primary and secondary National Ambient Air Quality Standards (NAAQS) for PM within the 2020 PM PA and were considered in EPA's final decision in the 2020 review to retain the PM NAAQS (see Section 1.3.5, (U.S. EPA, 2022)).

On June 10, 2021, EPA announced it is reconsidering the December 2020 decision to retain the PM NAAQS "because available scientific evidence and technical information indicate that the current standards may not be adequate to protect public health and welfare, as required by the Clean Air Act. EPA explained that as part of the reconsideration process " the agency will develop a supplement to the 2019 [PM ISA] that will take into account the most up-to-date science" (EPA Press Office, 2021).[5] As a result, the evidence presented within the 2019 PM ISA, along with the targeted identification and evaluation of new scientific information in this Supplement, provide the scientific basis to support a robust and thorough reconsideration of the 2020 PM NAAQS.

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[3] Consistent with the scope of the 2019 PM ISA (Section P.3.1), short-term exposures are defined as those exposures occurring over hours up to 1 month, whereas long-term exposures are defined as those exposures occurring over 1 month to years.

[4] Hereafter welfare effects refers to nonecological welfare effects, unless otherwise noted. The ecological effects resulting from the deposition of PM and PM components are being considered in a separate assessment as part of the review of the secondary (welfare-based) NAAQS for oxides of nitrogen, oxides of sulfur, and PM (U.S. EPA, 2020a).

[5] See Section 1.4 of the Policy Assessment for the Reconsideration of the National Ambient Air Quality Standards for Particulate Matter for additional details (U.S. EPA, 2022).

1.2. Rationale and Scope

In completing the review of the PM NAAQS in December 2020, EPA provisionally considered numerous studies published after the literature cutoff date (approximately January 2018) for the 2019 PM ISA. In reviewing these studies, as explained in *Responses to Significant Comments on the 2020 Proposed Decision on the National Ambient Air Quality Standards for Particulate Matter*, EPA "concluded that none of the studies materially change any of the broad scientific conclusions of the ISA regarding the health and welfare effects of PM or warrant reopening the air quality criteria for this review" (U.S. EPA, 2020c).

To inform the reconsideration of the PM NAAQS, EPA determined that a thorough evaluation is warranted of some studies that became available after the literature cutoff date of the 2019 PM ISA that could either further inform the adequacy of the current PM NAAQS or address key scientific topics that have evolved since the literature cutoff date for the 2019 PM ISA. Additionally, the evaluation of recent studies identified would occur in the form of a supplement and EPA would rely on the Supplement to the 2019 PM ISA and the 2019 PM ISA as the scientific foundation for the reconsideration, rather than revising the 2019 PM ISA or developing a new PM ISA. To facilitate the identification and evaluation of recent studies that warrant review, the developed a rationale (Section 1.2.1) and scope (Section 1.2.2) for this Supplement to the 2019 PM ISA to focus on specific PM-related health and welfare effects most pertinent to EPA in support of the reconsideration of the primary and secondary PM NAAQS. This targeted approach to developing the Supplement to the 2019 PM ISA for the purpose of reconsidering the 2020 PM NAAQS decision does not reflect a change to EPA's approach for developing ISAs for NAAQS reviews.

1.2.1. Rational for Inclusion of Health and Welfare Effects

The causality determinations presented within the 2019 PM ISA (discussed in Section 2), in combination with the characterization of the science with respect to the health and welfare effects of PM presented in the 2020 PM PA, form the basis of the rationale for the health and welfare effects evaluated within this Supplement. The following section provides specific details on the rationale for the types of evidence included, which ultimately forms the basis of the scope that governs the studies considered for inclusion in this Supplement.

In selecting the health effects to evaluate within this Supplement, the primary rationale is based on the causality determinations for health effect categories presented in the 2019 PM ISA, and the subsequent use of the health effects evidence in the 2020 PM PA (U.S. EPA, 2020b). "In considering the public health protection provided by the current primary $PM_{2.5}$ standards, and the protection that could be provided by alternatives, [EPA, within the 2020 PM PA] emphasized health outcomes for which the ISA determined that the evidence supports either a *causal* or a *likely to be causal relationship* with $PM_{2.5}$

exposures" (U.S. EPA, 2020b). Although the 2020 PM PA initially focused on this broader set of evidence, the basis of the discussion on potential alternative standards primarily focused on health effect categories for which the 2019 PM ISA concluded a *causal relationship* (i.e., short- and long-term $PM_{2.5}$ exposure and cardiovascular effects and mortality) as reflected in Figures 3-7 and 3-8 of the 2020 PM PA (U.S. EPA, 2020b). Therefore, within this Supplement the focus is only on the health effects evidence for which the 2019 PM ISA concluded a *causal relationship.*

In addition, this Supplement also considers recent health effects evidence that addresses key scientific topics for which the literature has evolved since the 2020 PM NAAQS review was completed, specifically since the literature cutoff date for the 2019 PM ISA. These key scientific topics include experimental studies conducted at near-ambient concentrations, epidemiologic studies that employed statistical approaches that attempt to more extensively account for confounders and are more robust to model misspecification (i.e., used alternative methods for confounder control)[6] or conducted accountability analyses, studies that assess the relationship between $PM_{2.5}$ exposure and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and coronavirus disease 2019 (COVID-19) death; and in accordance with recent EPA goals on addressing environmental justice [e.g., U.S. EPA (2021)], studies that examine disparities in $PM_{2.5}$ exposure and the risk of health effects by race/ethnicity and socioeconomic status (SES).

In identifying the studies to consider for inclusion within this Supplement, the focus was on those studies conducted in locations that were most informative to the reconsideration of the 2020 PM NAAQS. This criterion resulted in an assessment of the scientific literature that is more refined compared with the 2019 PM ISA. While the 2019 PM ISA considered and included studies conducted globally when evaluating the evidence and forming causality determinations, the rationale for the scope of this Supplement is directly informed by policy considerations surrounding the types of scientific information included in the 2020 PM PA. In addition to focusing on studies for health effect categories for which the 2019 PM ISA concluded *causal* or a *likely to be causal relationship*, as noted above, the 2020 PM PA also focused on a narrower set of studies conducted in locations that are most relevant to informing the level, form, averaging time, and indicator of the NAAQS for PM. Specifically, the 2020 PM PA states that the emphasis is on "multicity studies that examine health effect associations in the U.S. or Canada, as such studies examine potential associations over large geographic areas with diverse atmospheric conditions and population demographics (e.g., U.S. EPA (2019), Sections 11.1 and 11.2). Additionally, studies examining associations outside the U.S. or Canada reflect air quality and exposure patterns that may be less typical of the U.S., and thus less likely to be informative for purposes of reviewing the

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[6] In the peer-reviewed literature, these epidemiologic studies are often referred to as causal inference studies or studies that used causal modeling methods. For the purposes of this Supplement, this terminology is not used to prevent confusion with the main scientific conclusions (i.e., the causality determinations) presented within an ISA. In addition, as is consistent with the weight-of-evidence framework used within ISAs and discussed in the Preamble to the Integrated Science Assessments, an individual study on its own cannot inform causality, but instead represents a piece of the overall body of evidence.

NAAQS" (U.S. EPA, 2020b).[7] Therefore, within this Supplement the studies considered for inclusion are limited to those studies conducted in the U.S. and Canada. However, it is the combination of the scientific evidence detailed in the 2019 PM ISA and this Supplement that forms the complete scientific record informing the reconsideration of the 2020 PM NAAQS.

Consistent with the rationale for the health effects, the selection of welfare effects to evaluate within this Supplement is based on the causality determinations reported in the 2019 PM ISA and the subsequent use of scientific evidence in the 2020 PM PA. The 2019 PM ISA concluded a *causal relationship* for each of the welfare effects categories evaluated (i.e., visibility, climate effects, and materials effects). While the 2020 PM PA considered the broader set of evidence for these effects, for climate effects and material effects, it concluded that there remained "substantial uncertainties with regard to the quantitative relationships with PM concentrations and concentration patterns that limit[ed] [the] ability to quantitatively assess the public welfare protection provided by the standards from these effects" (U.S. EPA, 2020b). Given these uncertainties and limitations, the basis of the discussion on conclusions regarding the secondary standards in the 2020 PM PA primarily focused on visibility effects. Therefore, this Supplement focuses only on visibility effects in evaluating newly available scientific information, and consistent with the health effects rationale, is limited to studies conducted in the U.S. and Canada.

1.2.2.   Scope

Building on the rationale presented in Section 1.2.1, the scope of this Supplement provides specific criteria for the types of studies considered for inclusion within the Supplement. Specifically, studies must be peer reviewed and published between approximately January 2018 and March 2021, and satisfy the following criteria:

Health Effects

- U.S. and Canadian epidemiologic studies for health effect categories for which the 2019 PM ISA concluded a *causal relationship* (i.e., short- and long-term $PM_{2.5}$ exposure and cardiovascular effects and mortality)
    - U.S. and Canadian epidemiologic studies that employed alternative methods for confounder control or conducted accountability analyses (i.e., examined the effect of a policy on reducing $PM_{2.5}$ concentrations)[8]

Key Scientific Topics

- Experimental studies (i.e., controlled human exposure and animal toxicological) conducted at near-ambient $PM_{2.5}$ concentrations experienced in the U.S.

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[7] This emphasis on studies conducted in the U.S. or Canada is consistent with the approach in previous reviews of the PM NAAQS (U.S. EPA (2011), section 2.1.3).
[8]These studies do not include studies that instituted a specific action or intervention to reduce or mitigate exposure, such as the installation of high efficiency particle filters (HEPA) or indoor air cleaners.

- U.S.- and Canadian-based epidemiologic studies that examined the relationship between $PM_{2.5}$ exposures and SARS-CoV-2 infection and COVID-19 death

- At-risk populations

    o U.S.- and Canadian-based epidemiologic or exposure studies examining potential disparities in either $PM_{2.5}$ exposures or the risk of health effects by race/ethnicity or SES

    Welfare Effects

- U.S. and Canadian studies that provide new information on public preferences for visibility impairment and/or developed methodologies or conducted quantitative analyses of light extinction

Given the scope of this Supplement (i.e., not focusing on the broader body of experimental studies), it is important to recognize the evaluation conducted does not encompass the full multidisciplinary evaluation presented within the 2019 PM ISA as described in the *Preamble to the Integrated Science Assessments* (U.S. EPA, 2015) that would result in weight-of-evidence conclusions on causality (i.e., causality determinations). Additionally, this scope does not allow for the evaluation of recent studies for health effect categories from the 2019 PM ISA for which a *likely to be causal relationship* was concluded nor an assessment as to whether recent evidence may strengthen the causality determination to a *causal relationship*.[9] Therefore, this Supplement critically evaluates and provides key study-specific information for only those recent studies deemed to be of greatest significance for impending regulatory decisions regarding the PM NAAQS in the context of the body of evidence and scientific conclusions presented in the 2019 PM ISA. As such, the Supplement indicates whether recent evidence supports (is consistent with), supports and extends (is consistent with and reduces uncertainties), or does not support (is not consistent with) the causality determinations described in the 2019 PM ISA.

1.3. Development of the Supplement

The process used in developing this Supplement is consistent with the 2019 PM ISA as captured in the Preface and Appendix of the 2019 PM ISA. Because this Supplement builds on the 2019 PM ISA, that process is not reiterated but instead is cross referenced. Within the 2019 PM ISA, the Preface provides a detailed description of the process for developing ISAs (Section P.3.), including a discussion of the scope of the ISA (Section P.3.1.) and how evidence is evaluated (Section P.3.2.). A more detailed description of the process of evaluating evidence in ISAs is described in the Preamble to the Integrated Science Assessments (U.S. EPA, 2015) with information specific to the PM ISA in the Appendix of the 2019 PM ISA. Specifically, the Appendix describes in detail the various steps that encompassed the development of the PM ISA. These steps include the literature search and the evaluation of individual study quality, which details scientific considerations for evaluating the strength of inference from studies

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[9] The narrow scope also does not allow for the evaluation of recent studies for health effect categories from the 2019 PM ISA where *suggestive of, but not sufficient to infer, a causal relationship* and *inadequate to infer the presence or absence of a causal relationship* was concluded.

that examined the health effects of PM (2019 PM ISA, Section A.3.2., Table A-1). The information presented in Table A-1 in the 2019 PM ISA, which includes the identification and rationale behind advantageous study characteristics (e.g., study design, study population, exposure assessment) as well as information on the selection of results to present from individual studies, was relied upon in the process of considering and identifying recent studies evaluated within this Supplement.

1.4. Organization of the Supplement

The Supplement to the 2019 PM ISA is not intended to be a stand-alone document, but instead to build on the established scientific record regarding the health and welfare effects of PM presented in the 2019 PM ISA and prior assessments. As a result, this Supplement evaluates selected recent studies (i.e., studies published since the literature cutoff date of the 2019 PM ISA and that fall within the scope as outlined above) in the context of the scientific conclusions presented in the 2019 PM ISA.

This Supplement includes chapters and sections incorporated verbatim from the 2019 PM ISA to provide the background information and scientific conclusions necessary to put recent studies in the appropriate context. Section 2 of this Supplement consists of the Integrated Synthesis chapter (Chapter 1) of the 2019 PM ISA, which integrates and summarizes the overall scientific conclusions of the 2019 PM ISA. Section 3 represents the evaluation of the health effects evidence (i.e., short- and long-term $PM_{2.5}$ exposure and cardiovascular effects and mortality) that falls within the scope of this Supplement. The organization of Section 3 is consistent with the overall organization of the health effects discussion in the 2019 PM ISA, which includes separate discussions of the evidence organized in relation to exposure duration (i.e., short- or long-term exposure) and then within the exposure duration sections discussions organized around specific health effects (e.g., myocardial infarction, nonaccidental mortality) and specific issues of importance (e.g., copollutant confounding, concentration-response relationship). In addition, within each section of Section 3, the summary and causality determination from the 2019 PM ISA is presented to capture the scientific conclusions of the ISA, which recent literature builds upon. The sections that follow in Section 3 evaluate and integrate the evidence from recent studies and ultimately assess the results of recent studies in the context of the causality determinations presented in the 2019 PM ISA. Additionally, Section 3 evaluates recent studies that assess key science topics that have evolved since the completion of the 2019 PM ISA. Study-specific details for the epidemiologic studies evaluated in Section 3, such as information on study population, exposure assessment, $PM_{2.5}$ concentrations, and confounder control (e.g., copollutants) are detailed in tables presented in Section 3. Section 4 consists of an evaluation of recent studies that inform visibility effects and is organized similar to the health effects chapter. Therefore, Section 4 first presents the summary and causality determination from the 2019 PM ISA, then evaluates recent studies, and concludes by assessing new evidence in the context of the conclusions for visibility impairment presented in the 2019 PM ISA. Finally, Section 5 provides a summary and presents overarching conclusions based on the evaluation of recent studies within this Supplement.

2. OVERVIEW OF MAIN CONCLUSIONS OF THE 2019 INTEGRATED SCIENCE ASSESSMENT FOR PARTICULATE MATTER

Overall Conclusions of the 2019 Particulate Matter (PM) Integrated Science Assessment (ISA)

- Evidence spanning scientific disciplines (i.e., atmospheric chemistry, exposure science, dosimetry, epidemiology, controlled human exposure, and animal toxicology) built upon evidence detailed in the 2009 PM ISA and reaffirmed a *causal relationship* between short- and long-term $PM_{2.5}$ exposure and cardiovascular effects and total (nonaccidental) mortality, and a *likely to be causal relationship* for respiratory effects.
- Experimental and epidemiologic evidence supported a *likely to be causal relationship* between long-term $PM_{2.5}$ exposure and nervous system effects.
- Evidence, primarily from studies of lung cancer incidence and mortality, in combination with the decades of research on the mutagenicity and carcinogenicity of PM supported a *likely to be causal relationship* between long-term $PM_{2.5}$ exposure and cancer.
- Remaining uncertainties and limitations in the scientific evidence contributed to a *suggestive of, but not sufficient to infer, a causal relationship* and *inadequate to infer the presence or absence of a causal relationship* for all other exposure, size fraction, and health effects category combinations.
- Evidence built upon and reaffirmed that there is a *causal relationship* between PM and the nonecological welfare effects: visibility impairment, climate effects, and materials effects.
- The assessment of PM sources and components confirmed and continued to support the conclusion from the 2009 PM ISA: *Many $PM_{2.5}$ components and sources are associated with many health effects, and the evidence does not indicate that any one source or component is more strongly related with health effects than $PM_{2.5}$ mass*.
- Many populations (e.g., healthy, diseased) and lifestages (e.g., children, older adults) have been shown to be at risk of a health effect in response to short- or long-term PM exposure, particularly $PM_{2.5}$. However, of the populations and lifestages examined, scientific evidence indicated that only some populations may be at <u>*disproportionately increased risk*</u> of a $PM_{2.5}$-related health effect, including minority populations (often defined as non-White populations within individual studies), children, people with specific genetic variants in genes in the glutathione transferase pathway, people who are overweight or obese, people with preexisting cardiovascular and respiratory diseases, people of low socioeconomic status (SES), and people who smoke or were former smokers. Inadequate evidence exists to determine whether having diabetes, being in an older lifestage (i.e., older adults), residential location (including proximity to source and urban residence), sex, or diet increase the risk of $PM_{2.5}$-related health effects.

2.1. Health Effects

The 2019 Integrated Science Assessment for Particulate Matter (2019 PM ISA) evaluated relationships between short-term and long-term exposures to PM (i.e., $PM_{2.5}$, $PM_{10-2.5}$, and UFPs) and an array of health effects described in epidemiologic, controlled human exposure, and animal toxicological studies. In the assessment of the overall evidence, the strengths and limitations of individual studies were evaluated based on scientific considerations detailed in the Appendix to the 2019 PM ISA. Short-term exposures are defined as those with durations of hours up to 1 month, with most studies examining effects related to exposures in the range of 24 hours to 1 week. Long-term exposures are defined as those with

durations of more than 1 month to years. As detailed in the Preface of the 2019 PM ISA, the evaluation of the health effects evidence focuses on exposures conducted at concentrations of PM that are relevant to the range of human exposures across ambient microenvironments (up to 2 mg/m^3, which is one to two orders of magnitude above ambient concentrations), and studies that (1) include a composite measure of PM[10] or (2) apply some approach to assess the direct effect of a specific PM size-fraction when the exposure of interest is a source-based mixture (e.g., diesel exhaust, gasoline exhaust, wood smoke).

Consistent with the Integrated Synthesis chapter (Chapter 1) of the 2019 PM ISA, the subsequent sections and accompanying table (Table 2-2) summarize the key evidence that informed the causality determinations for relationships between PM exposure and health effects detailed in the 2019 PM ISA, specifically those relationships for which it was determined that a *causal* or *likely to be causal relationship* exists (Table 2-1). While the following sections of this chapter focus on health effects categories for which the evidence supported a *causal* or *likely to be causal relationship,* this Supplement as reflected in the Scope (Section 1.2.2) focuses on a narrower evidence base in subsequent chapters. These causality determinations draw from evidence related to the biological plausibility of PM-related health effects and the broader health effects evidence described in detail within the 2019 PM ISA in Chapter 5−Chapter 11, as well as information on dosimetry in Chapter 4 and exposure assessment in Chapter 3. Those relationships between PM and health effects for which the 2019 PM ISA concluded that the evidence supported a causality determination of *suggestive of, but not sufficient to infer, a causal relationship* or *inadequate to infer the presence or absence of a causal relationship* are not discussed within this chapter, but are more fully discussed in the 2019 PM ISA.

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[10]Composite measures of PM may include mass, volume, surface area, or number concentration.

Table 2-1   *Causal* and *likely to be causal* causality determinations for short- and long-term PM$_{2.5}$ exposure.

Size Fraction	Health Effects Category	Exposure Duration	Causality Determination	Section
PM$_{2.5}$	Respiratory	Short-term	Likely to be causal	2.1.1.1.1
		Long-term	Likely to be causal	2.1.1.1.2
	Cardiovascular	Short-term	Causal	2.1.1.2.1
		Long-term	Causal	2.1.1.2.2
	Nervous system	Long-term	Likely to be causal	2.1.1.3.1
	Cancer	Long-term	Likely to be causal	2.1.1.4.1
	Mortality	Short-term	Causal	2.1.1.5.1
		Long-term	Causal	2.1.1.5.2

PM$_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm.

2.1.1.   Health Effects of PM$_{2.5}$

Substantial scientific evidence exists across disciplines (i.e., animal toxicology, controlled human exposure, and epidemiology) showing that both short- and long-term PM$_{2.5}$ exposure can result in a range of health effects, from changes in circulating biomarkers to mortality. However, the strength of the PM$_{2.5}$ exposure−health effects relationship varies depending on the exposure duration (i.e., short- or long-term) and broad health effects category (e.g., cardiovascular effects, respiratory effects) examined. Across the broad health effects categories examined in the 2019 PM ISA, the evidence supporting biological plausibility varies, but generally includes modulation of the autonomic nervous system and inflammation as part of the pathways leading to overt health effects. Discussions of subsequent events that could occur due to deposition of inhaled PM$_{2.5}$ in the respiratory tract are detailed in the biological plausibility sections of each health chapter in the 2019 PM ISA and summarized in the following sections.

2.1.1.1.   Respiratory Effects

Scientific evidence presented in the 2019 PM ISA continues to support the conclusion of the 2009 PM ISA that there is a *likely to be causal relationship* between both short- and long-term PM$_{2.5}$ exposure and respiratory effects. These causality determinations are based on the consistency of findings within disciplines; the coherence of evidence across disciplines, including epidemiologic and animal toxicological studies, with more limited evidence from controlled human exposure studies; and the

evidence supporting biologically plausible pathways for respiratory effects, such as asthma exacerbation, development of asthma, chronic obstructive pulmonary disease (COPD) exacerbation, and respiratory mortality.

2.1.1.1.1.   Respiratory Effects Associated with Short-Term PM$_{2.5}$ Exposure

Epidemiologic studies provide strong evidence for overt respiratory effects, including respiratory-related emergency department (ED) visits and hospital admissions and respiratory mortality associated with short-term PM$_{2.5}$ exposure, with coherence provided by some evidence of respiratory effects from experimental studies. Collectively this evidence supported the conclusion of the 2009 PM ISA that there is a *likely to be causal relationship* between short-term PM$_{2.5}$ exposure and respiratory effects (Table 2-2). This conclusion is based on multiple epidemiologic studies demonstrating generally consistent, positive associations with ED visits and hospital admissions for asthma, COPD, and combined respiratory-related diseases, as well as with respiratory mortality. Evidence from animal toxicological studies, although limited, was supportive of and provided biological plausibility for the associations observed in the epidemiologic studies related to exacerbation of asthma and COPD as well as respiratory infection.

Epidemiologic studies evaluated in the 2019 PM ISA continue to provide strong evidence for a relationship between short-term PM$_{2.5}$ exposure and several respiratory-related endpoints, including asthma exacerbation (2019 PM ISA, Section 5.1.2.1), COPD exacerbation (2019 PM ISA, Section 5.1.4.1), and combined respiratory-related diseases (2019 PM ISA, Section 5.1.6), particularly from studies examining ED visits and hospital admissions. The consistent positive associations between short-term PM$_{2.5}$ exposure and asthma and COPD ED visits and hospital admissions across studies that used different approaches to control for the potential confounding effects of weather (e.g., temperature) are supported by epidemiologic studies demonstrating associations with other respiratory-related effects, such as symptoms and medication use that are indicative of asthma and COPD exacerbations (2019 PM ISA, Section 5.1.2.2 and Section 5.1.4.2). The collective body of epidemiologic evidence for asthma exacerbation was more consistent in children than in adults. Epidemiologic studies examining the relationship between short-term PM$_{2.5}$ exposure and respiratory mortality provided evidence of consistent positive associations, indicating a continuum of effects from morbidity to mortality (2019 PM ISA, Section 5.1.9).

Building off the studies evaluated in the 2009 PM ISA, epidemiologic studies evaluated in the 2019 PM ISA expanded the assessment of potential copollutant confounding. There was some evidence that PM$_{2.5}$ associations with asthma exacerbation, combined respiratory-related diseases, and respiratory mortality remain relatively unchanged in copollutant models with gaseous pollutants (i.e., O$_3$, NO$_2$, SO$_2$, with more limited evidence for CO) and other particle sizes (i.e., PM$_{10–2.5}$) (2019 PM ISA, Section 5.1.10.1). The uncertainty as to whether there is an independent effect of PM$_{2.5}$ on respiratory health, was partially addressed by findings from animal toxicological studies.

Animal toxicological studies of short-term $PM_{2.5}$ exposure provided coherence and biological plausibility for asthma and COPD exacerbations by demonstrating asthma-related responses in an animal model of allergic airways disease and enhanced lung injury and inflammation in an animal model of COPD (2019 PM ISA, Section 5.1.2.4.4 and Section 5.1.4.4.3). There was also a broad body of animal toxicological studies examining respiratory effects due to short-term $PM_{2.5}$ exposure, but most of this evidence was from studies conducted in healthy animals, and therefore, does not provide coherence with the results of epidemiologic studies examining effects in people with asthma or COPD. This evidence base also provided consistent evidence for respiratory irritant effects; limited evidence for altered host defense, greater susceptibility to bacterial infection, and allergic sensitization; and some evidence for pulmonary injury, inflammation, and oxidant stress. Controlled human exposure studies conducted in people with asthma or COPD provided minimal evidence of effects due to short-term $PM_{2.5}$ exposure, such as decrements in lung function and pulmonary inflammation. These studies are limited in terms of endpoints evaluated and the size and health status of study subjects.

2.1.1.1.2.   Respiratory Effects Associated with Long-Term $PM_{2.5}$ Exposure

Epidemiologic studies provided strong evidence for effects on lung development, with additional evidence for the development of asthma in children due to long-term $PM_{2.5}$ exposure. Evidence from animal toxicological studies, although limited, was supportive of and provided biological plausibility for the associations reported in epidemiologic studies related to lung development and the development of asthma. There was also epidemiologic evidence supporting a decline in lung function in adults in response to long-term $PM_{2.5}$ exposure. Collectively this evidence supported the conclusions of the 2009 PM ISA that there is a *likely to be causal relationship* between long-term $PM_{2.5}$ exposure and respiratory effects (Table 2-2).

Epidemiologic studies evaluated in the 2019 PM ISA continued to support an association between long-term $PM_{2.5}$ exposure and several respiratory-related endpoints in children and adults. In children, studies in multiple cohorts provided strong evidence for decrements in lung function growth (2019 PM ISA, Section 5.2.2.1.1). Robust and persistent effects were observed across study locations, exposure assessment methods, and time periods. An animal toxicological study demonstrating impaired lung development resulting from pre- and postnatal $PM_{2.5}$ exposure provided biological plausibility for these findings (2019 PM ISA, Section 5.2.2.1.2). Results of prospective cohort studies in children also provided some evidence for asthma development in children and are supported by other studies examining asthma prevalence in children, childhood wheeze, and pulmonary inflammation (2019 PM ISA, Section 5.2.3). Biological plausibility was provided by an animal toxicological study of long-term $PM_{2.5}$ exposure demonstrating the development of an allergic phenotype and increase in airway responsiveness (2019 PM ISA, Section 5.2.3.3.2). There was limited evidence of increased bronchitic symptoms and hospitalization in children with asthma in relation to long-term $PM_{2.5}$ exposure (2019 PM ISA, Section 5.2.7). In adults, long-term $PM_{2.5}$ exposure was found to be associated with accelerating lung function decline (2019 PM

ISA, Section 5.2.2.2.2). Consistent evidence was observed for respiratory mortality and cause-specific respiratory mortality for COPD and respiratory infection (2019 PM ISA, Section 5.2.10), providing evidence of a continuum of effects in response to long-term $PM_{2.5}$ exposure.

Only a few epidemiologic studies evaluated in the 2019 PM ISA have further examined potential copollutant confounding. There was some evidence that $PM_{2.5}$ associations with respiratory mortality remained robust in models with some gaseous pollutants (2019 PM ISA, Section 5.2.10); however, there was limited assessment of potential copollutant confounding when examining respiratory morbidity outcomes. The uncertainty related to the independence of $PM_{2.5}$ effects was partially addressed by findings of animal toxicological studies. Long-term exposure to $PM_{2.5}$ resulted in oxidative stress, inflammation, and morphologic changes in both upper and lower airways (2019 PM ISA, Section 5.2.8), in addition to the asthma-related and lung development-related effects mentioned above. Epidemiologic studies examining the effects of declining $PM_{2.5}$ concentrations provided additional support for a relationship between long-term $PM_{2.5}$ exposure and respiratory health by demonstrating improvements in lung function growth and bronchitic symptoms in children, and improvement in lung function in adults in association with declining $PM_{2.5}$ concentrations (2019 PM ISA, Section 5.2.11). However, the limited examination of copollutant confounding in studies of declining $PM_{2.5}$ concentrations was a notable uncertainty given the corresponding decline in other pollutants over the time period of the evaluated studies.

2.1.1.2.   Cardiovascular Effects

Consistent with the conclusions of the 2009 PM ISA, more recently published scientific evidence further strengthens the conclusion that there is a *causal relationship* between both short- and long-term $PM_{2.5}$ exposure and cardiovascular effects. These causality determinations are based on the consistency of findings within disciplines; coherence among evidence from controlled human exposure, epidemiologic, and animal toxicological studies; and evidence supporting biologically plausible pathways for cardiovascular effects, such as reduced myocardial blood flow, altered vascular reactivity, myocardial infarctions, and cardiovascular mortality.

2.1.1.2.1.   Cardiovascular Effects Associated with Short-Term $PM_{2.5}$ Exposure

Strong evidence from epidemiologic studies demonstrating associations between cardiovascular ED visits and hospital admissions in combination with evidence for $PM_{2.5}$-induced cardiovascular effects from controlled human exposure and animal toxicological studies confirmed and extended the conclusion of a *causal relationship* between short-term $PM_{2.5}$ exposure and cardiovascular effects from the 2009 PM ISA (Table 2-2). This conclusion was based on multiple epidemiologic studies demonstrating associations with cardiovascular effects such as ischemic heart disease (IHD)- and heart failure (HF)-related ED visits

and hospital admissions, as well as cardiovascular mortality. The epidemiologic evidence was supported by experimental studies demonstrating endothelial dysfunction, changes in blood pressure (BP), and alterations in heart function in response to short-term $PM_{2.5}$ exposure. Additional evidence from epidemiologic, controlled human exposure, and animal toxicological studies also provided ample evidence of biologically plausible pathways by which short-term exposure to $PM_{2.5}$ can result in overt cardiovascular effects.

Consistent with the 2009 PM ISA, the strongest evidence comes from epidemiologic studies that reported consistent positive associations between short-term $PM_{2.5}$ exposure and cardiovascular-related ED visits and hospital admissions particularly for IHD (2019 PM ISA, Section 6.1.2.1) and HF (2019 PM ISA, Section 6.1.3.1), as well as cardiovascular-related mortality (2019 PM ISA, Section 6.1.9) across studies that used different approaches to control for the potential confounding effects of weather (e.g., temperature). While associations remained relatively unchanged across the copollutants evaluated, the evidence was especially consistent for air pollutants that are not typically associated with traffic (i.e., ozone, SO_2, $PM_{10-2.5}$). In some instances, associations in copollutant models were attenuated, but this was only observed for the traffic-related pollutants (i.e., NO_2, CO), which generally had higher correlations with $PM_{2.5}$ than other copollutants. This evidence from copollutant analyses from studies evaluated in the 2019 PM ISA generally indicates that the associations observed between short-term $PM_{2.5}$ exposure and cardiovascular effects are not artifacts due to confounding by another air pollutant (2019 PM ISA, Section 6.1.14.1). These epidemiologic studies reduce a key uncertainty identified in the 2009 PM ISA by providing evidence that gaseous pollutants are not likely to confound the $PM_{2.5}$-cardiovascular effects relationship.

The independence of $PM_{2.5}$ effects is further addressed by findings of controlled human exposure and animal toxicological studies evaluated in the 2019 PM ISA. The most consistent evidence from controlled human exposure studies was for a $PM_{2.5}$ effect on endothelial function (2019 PM ISA, Section 6.1.13). Multiple recent controlled human exposure studies reported that $PM_{2.5}$ impaired some measure of vessel dilation following reactive hyperemia or pharmacological challenge relative to filtered air. Given the relationship between endothelial function and BP, these results were coherent with multiple controlled human exposure studies that reported changes in BP following short-term $PM_{2.5}$ concentrated ambient particles (CAPs) exposure (2019 PM ISA, Section 6.1.6.3). However, these results were inconsistent with some controlled human exposure studies from previous reviews that did not find changes in endothelial function or BP. The results of controlled human exposure studies evaluated in the 2019 PM ISA are also coherent with evidence from animal toxicological studies demonstrating endothelial dysfunction and changes in BP or the renin angiotensin system following short-term $PM_{2.5}$ exposure (2019 PM ISA, Section 6.1.13.3 and Section 6.1.6.4). Moreover, changes in endothelial function and BP reported in recent experimental studies were consistent with epidemiologic studies reporting associations between short-term $PM_{2.5}$ exposure and IHD, as well as with limited epidemiologic panel study evidence of associations with BP. In addition, animal toxicological studies demonstrating that short-term $PM_{2.5}$ exposure results in decreased cardiac contractility and changes in left ventricular

pressure were coherent with epidemiologic studies reporting associations between short-term $PM_{2.5}$ exposure and HF.

Collectively, the evidence from controlled human exposure, animal toxicological, and epidemiologic panel studies provided a biologically plausible pathway by which short-term $PM_{2.5}$ exposure could result in cardiovascular effects such as those leading to an ED visit, hospital admission, or mortality. This proposed pathway (2019 PM ISA, Section 6.1.1) begins with pulmonary inflammation and/or activation of sensory nerves in the respiratory track and progresses to autonomic nervous system imbalance and/or systemic inflammation that can potentially affect cardiovascular endpoints such as endothelial function, heart rate variability (HRV), hemostasis, and/or BP. Changes in the aforementioned cardiovascular endpoints may then lead to the development of arrhythmia, thrombosis, and/or acute myocardial ischemia, potentially resulting in outcomes such as myocardial infarction, IHD, HF, and possibly death.

Overall, across the scientific disciplines, recent studies extended and supported the previous evidence for a continuum of cardiovascular-related health effects following short-term exposure to $PM_{2.5}$. These effects range from relatively modest increases in biomarkers related to inflammation, to subclinical cardiovascular endpoints such as endothelial dysfunction, the overt outcomes of ED visits and hospital admissions, specifically for IHD and HF, and ultimately cardiovascular-related mortality.

2.1.1.2.2.   Cardiovascular Effects Associated with Long-Term $PM_{2.5}$ Exposure

Multiple epidemiologic studies evaluated in the 2019 PM ISA and previous assessments that extensively control for potential confounders provided strong evidence of positive associations with cardiovascular mortality, which in combination with supporting evidence from recent studies examining cardiovascular morbidity reaffirmed the conclusion of a *causal relationship* between long-term $PM_{2.5}$ exposure and cardiovascular effects in the 2009 PM ISA (Table 2-2). This conclusion was based on U.S. and Canadian cohort studies evaluated in the 2019 PM ISA that demonstrated consistent, positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality, with more limited evidence from studies examining long-term $PM_{2.5}$ exposure and cardiovascular morbidity.

Epidemiologic studies consisting of U.S.-based cohorts and subsequent analyses of these cohorts, provided the basis of the conclusions in the 2009 PM ISA. These studies, in combination with cohort studies evaluated in the 2019 PM ISA, continued to demonstrate consistent, positive associations and support a strong relationship between long-term $PM_{2.5}$ exposure and cardiovascular mortality. The results of these cohort studies are consistent across various spatial extents, exposure assessment techniques, and statistical techniques in locations where mean annual average concentrations are near or below 12 micrograms per cubic meter ($\mu g/m^3$) (2019 PM ISA, Section 6.2.10).

The body of literature examining the relationship between long-term $PM_{2.5}$ exposure and cardiovascular morbidity has greatly expanded since the 2009 PM ISA. Epidemiologic studies evaluated in the 2019 PM ISA examining cardiovascular morbidity endpoints consisted of several large U.S. cohort studies each focusing on populations with distinct demographic characteristics (e.g., postmenopausal women, male doctors) and extensive consideration of potential confounders. These studies have reported heterogeneous results, with several studies that adjusted for important confounders, including socioeconomic status (SES), reporting positive associations for cardiovascular morbidity endpoints. The strong associations reported between long-term $PM_{2.5}$ exposure and coronary events (e.g., coronary heart disease [CHD] and stroke) among postmenopausal women in the Women's Health Initiative (WHI) cohort, highlighted in 2009 PM ISA, were strengthened in an extended analysis that considered individual and neighborhood-level SES (2019 PM ISA, Section 6.2.3; Section 6.2.10). Recent analyses of other cohorts of women (i.e., Nurses' Health Study [NHS], California Teachers Study [CTS]) that were comparable to WHI in that they considered menopausal status or hormone replacement therapy did not show consistent positive associations with CHD, myocardial infarction, or stroke. Longitudinal studies demonstrated that changes in the progression of atherosclerosis in relation to long-term exposure to $PM_{2.5}$ were variable across cohorts and found to depend, in part, on the vascular bed in which atherosclerosis was evaluated (2019 PM ISA, Section 6.2.4.1). However, within a study focusing on the progression of atherosclerosis in a healthy population, the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA-Air), an association was observed between long-term $PM_{2.5}$ exposure and coronary artery calcification (CAC), which is a strong predictor of CHD (2019 PM ISA, Section 6.2.4). A small number of studies reported positive associations between long-term $PM_{2.5}$ exposure and HF, BP changes, and hypertension. Longitudinal epidemiologic analyses also supported the observation of positive associations with markers of systemic inflammation, coagulation, and endothelial dysfunction. These HF studies were coherent with animal toxicological studies demonstrating decreased contractility and cardiac output and increased coronary artery wall thickness following long-term $PM_{2.5}$ exposure (2019 PM ISA, Section 6.2.4.2). Moreover, animal toxicological studies finding a relationship between long-term exposure to $PM_{2.5}$ and changes in BP in rats and mice were coherent with epidemiologic studies reporting positive associations between long-term exposure to $PM_{2.5}$ and hypertension. Similarly, evidence of atherosclerotic plaque progression in a genetically susceptible mouse model was consistent with epidemiologic studies reporting associations between atherosclerosis and long-term $PM_{2.5}$ exposure.

The body of evidence evaluated in the 2019 PM ISA also reduced uncertainties identified in the 2009 PM ISA related to potential copollutant confounding and the shape of the concentration-response (C-R) relationship for cardiovascular disease (CVD) effects following long-term $PM_{2.5}$ exposure. Generally, most of the $PM_{2.5}$ effect estimates relating long-term $PM_{2.5}$ exposure to cardiovascular mortality remained relatively unchanged or increased in copollutant models adjusted for O_3, NO_2, SO_2, and $PM_{10-2.5}$ (2019 PM ISA, Section 6.2.15). In addition, most of the results from analyses examining the C-R function for cardiovascular mortality supported a linear, no-threshold relationship for cardiovascular mortality, especially at mean annual $PM_{2.5}$ concentrations ≤ 12 $\mu g/m^3$ (2019 PM ISA, Section 6.2.10). Some studies reported that the slope of the C-R curve tended to be steeper at lower concentrations,

especially for IHD mortality, suggesting a supralinear C-R relationship. A limited number of cardiovascular morbidity studies examined the shape of the C-R relationship and generally reported a steeper C-R curve at lower concentrations (starting at ~10 µg/m^3) with the slope of the C-R curve decreasing at higher PM$_{2.5}$ concentrations (2019 PM ISA, Section 6.2.16).

Evidence from animal toxicological and epidemiologic studies also provided biologically plausible pathways by which long-term PM$_{2.5}$ exposure could lead to cardiovascular effects such as CHD, stroke, and CVD-related mortality (2019 PM ISA, Section 6.2.1). These pathways initially involve autonomic nervous system changes and/or systemic inflammation that can potentially affect endpoints related to vascular function, altered hemostasis, hypertension, atherosclerotic plaque progression, and arrhythmia. Changes in cardiovascular endpoints such as these may then lead to IHD, HF, and possibly death.

Overall, there was consistent evidence from multiple epidemiologic studies that long-term exposure to PM$_{2.5}$ is associated with cardiovascular mortality. Associations with CHD, stroke, and atherosclerosis progression were observed in several recent epidemiologic studies providing coherence for PM$_{2.5}$-related cardiovascular mortality. Results from copollutant models generally support the independence of PM$_{2.5}$ associations. Additional evidence of the direct effect of PM$_{2.5}$ on the cardiovascular system was provided by experimental studies in animals demonstrating effects including atherosclerosis plaque progression and changes in cardiac contractility and BP.

2.1.1.3.   Nervous System Effects

2.1.1.3.1.   Nervous System Effects Associated with Long-Term PM$_{2.5}$ Exposure

The 2009 PM ISA evaluated a small number of animal toxicological studies pertaining to the effects of long-term exposures to PM$_{2.5}$ on the nervous system. Since the 2009 PM ISA, the literature base has greatly expanded with studies evaluated in the 2019 PM ISA providing new information that strengthens the lines of evidence indicating that long-term PM$_{2.5}$ exposure may lead to effects on the brain that are associated with neurodegeneration (i.e., neuroinflammation and reductions in brain volume), as well as cognitive effects in older adults (Table 2-2). Animal toxicological studies provided evidence for a range of nervous system effects including neuroinflammation and oxidative stress, neurodegeneration, cognitive effects, and effects on neurodevelopment. Although the epidemiologic evidence was more limited in terms of the number of studies conducted, multiple studies generally supported associations between long-term PM$_{2.5}$ exposure and changes in brain morphology, cognitive decrements, and dementia in adult populations. The consistency and coherence of the evidence across disciplines as it relates to region-specific brain inflammation, morphologic changes in the brain, cognitive effects, and dementia in adult populations supported that there is a *likely to be causal relationship* between long-term PM$_{2.5}$

exposure and nervous system effects. Thus, the expanded evidence base allowed for the first-time, a causality determination for long-term $PM_{2.5}$ exposure and nervous system effects.

There was strong evidence for biologically plausible pathways that may underlie nervous system effects resulting from long-term exposure to $PM_{2.5}$. Studies demonstrated modulation of the autonomic nervous system leading to downstream consequences including cardiovascular effects (2019 PM ISA, Section 6.2.1). In addition, the pathway involving neuroinflammation in specific regions of the brain (i.e., the hippocampus, cerebral cortex, and hypothalamus) and morphologic changes in the brain indicative of neurodegeneration, is well substantiated and coherent across animal toxicological and epidemiologic studies (2019 PM ISA, Section 8.2.3 and Section 8.2.4). Specifically, morphologic changes induced in the hippocampus of animals were accompanied by impaired learning and memory and there was consistent evidence from multiple epidemiologic studies that long-term $PM_{2.5}$ exposure is associated with reduced cognitive function (2019 PM ISA, Section 8.2.5). Further, the presence of early markers of Alzheimer's disease pathology was demonstrated in animals following long-term exposure to $PM_{2.5}$ CAPs, which was consistent with a small number of epidemiologic studies that reported positive associations with neurodegenerative changes in the brain (i.e., decreased brain volume) and Alzheimer's disease or all-cause dementia (2019 PM ISA, Section 8.2.6). Although the loss of dopaminergic neurons in the substantia nigra, which is a hallmark of Parkinson's disease, was demonstrated in animals (2019 PM ISA, Section 8.2.4), epidemiologic studies did not report associations with Parkinson's disease (2019 PM ISA, Section 8.2.6). Overall, the lack of consideration of copollutant confounding introduces some uncertainty in the interpretation of the epidemiologic studies but this uncertainty was addressed, in part, by the direct evidence of effects provided by animal toxicological studies.

In addition to the findings described above, which are mostly relevant to adults, several recent studies of neurodevelopmental effects in children have also been conducted. Positive associations between long-term exposure to $PM_{2.5}$ during the prenatal period and autism spectrum disorder (ASD) were consistently observed across multiple epidemiologic studies (2019 PM ISA, Section 8.2.7.2). However, several studies of performance on tests of cognitive function provided little support for an association. Overall, these epidemiologic studies of developmental effects were limited due to their lack of control for potential confounding by copollutants, the small number of studies, and uncertainty regarding critical exposure windows. A study in animals that found inflammatory and morphologic changes in the corpus collosum and hippocampus, as well as ventriculomegaly in young animals following prenatal exposure to $PM_{2.5}$ CAPs provided initial evidence indicating a potential biologically plausible pathway for a relationship between $PM_{2.5}$ and ASD.

2.1.1.4.   Cancer

2.1.1.4.1.   Cancer Associated with Long-Term PM$_{2.5}$ Exposure

Experimental and epidemiologic evidence indicating genotoxicity, epigenetic effects (e.g., DNA methylation), and increased carcinogenic potential due to PM$_{2.5}$ exposure, along with strong epidemiologic evidence for increases in lung cancer incidence and mortality, supported a *likely to be causal relationship* between long-term PM$_{2.5}$ exposure and cancer (Table 2-2). This causality determination represented a change from the *suggestive of a causal relationship*[11] determination reported in the 2009 PM ISA. The evidence base underlying this conclusion encompasses the decades of research on whole PM exposures and research evaluated in the 2019 PM ISA focusing specifically on PM$_{2.5}$.

PM$_{2.5}$ exhibits various characteristics of carcinogens, as shown in studies demonstrating genotoxic effects (e.g., DNA damage), epigenetic alterations, oxidative stress, and electrophilicity. The examination of the role of PM$_{2.5}$ in cancer development has often focused on whether whole PM, not specific size fractions, has mutagenic properties and whether exposure to whole PM results in genotoxicity or carcinogenicity. Additionally, it has been well characterized that some components of PM$_{2.5}$, specifically hexavalent chromium, nickel, arsenic, and polycyclic aromatic hydrocarbons are known human carcinogens. Extensive analyses of PM$_{2.5}$ and PM$_{2.5}$ extracts in the Ames *Salmonella*/mammalian-microsome mutagenicity assay demonstrated that PM$_{2.5}$ contains mutagenic agents (2019 PM ISA, Section 10.2.2.1). Additional in vitro and in vivo toxicological studies indicated the potential for PM$_{2.5}$ exposure to result in DNA damage, which was supported by limited human evidence (2019 PM ISA, Section 10.2.2.2). Some studies have also demonstrated that PM$_{2.5}$ exposure can result in cytogenetic effects, specifically micronuclei formation and chromosomal aberrations (2019 PM ISA, Section 10.2.2.3), as well as differential expression of genes potentially relevant to genotoxicity or other aspects of cancer pathogenesis (2019 PM ISA, Section 10.2.2.4). Although inconsistently examined across studies, changes in cellular and molecular markers of genotoxicity and epigenetic alterations, which may lead to genomic instability, are demonstrated in response to PM$_{2.5}$ exposure. Further, the carcinogenic potential of PM$_{2.5}$ was demonstrated in an animal toxicological study in which chronic inhalation enhanced tumor formation that was initiated by exposure to urethane (2019 PM ISA, Section 10.2.4). Additionally, epidemiologic studies evaluated in the 2019 PM ISA encompassing multiple cohorts that are diverse in terms of both geographic coverage and population characteristics have provided evidence of primarily consistent positive associations between long-term PM$_{2.5}$ exposure and lung cancer incidence and mortality, particularly in never smokers (2019 PM ISA, Section 10.2.5.1). Experimental and epidemiologic evidence of genotoxicity, epigenetic effects, and carcinogenic potential provides biological plausibility for epidemiologic results of lung cancer incidence and mortality. Although evaluated in a limited number of studies, the assessment of potential copollutant confounding,

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[11]Since the 2009 PM ISA, the causality determination language has been updated and this category is now stated as *suggestive of, but not sufficient to infer, a causal relationship.*

particularly with O_3, indicated that $PM_{2.5}$ associations with lung cancer incidence and mortality are relatively unchanged in copollutant models (2019 PM ISA, Section 10.2.5.1.3). There was limited evidence that long-term $PM_{2.5}$ exposure is associated with cancers in other organ systems; however, there was initial evidence that $PM_{2.5}$ exposure may reduce survival in individuals with cancer.

2.1.1.5.   Mortality

Consistent with the conclusions of the 2009 PM ISA, evidence from studies evaluated in the 2019 PM ISA reaffirmed and further strengthened that there is a *causal relationship* between both short- and long-term $PM_{2.5}$ exposure and total mortality. These causality determinations were based on the consistency of findings across a large body of epidemiologic studies. Evidence from controlled human exposure, epidemiologic, and animal toxicological studies of respiratory and cardiovascular morbidity also provided coherence, as well as biological plausibility. Together, the consistency and coherence in the evidence collectively supported a continuum of effects by which short- and long-term $PM_{2.5}$ exposure could result in mortality.

2.1.1.5.1.   Mortality Associated with Short-Term $PM_{2.5}$ Exposure

Strong epidemiologic evidence from studies evaluated in the 2019 PM ISA, as well as in previous assessments, that examined total (nonaccidental) mortality in combination with evidence for cause-specific respiratory and cardiovascular mortality continued to support the conclusion of the 2009 PM ISA that there is a *causal relationship* between short-term $PM_{2.5}$ exposure and total (nonaccidental) mortality (Table 2-2). This conclusion was based on multiple recent multicity studies conducted in the U.S., Canada, Europe, and Asia that continued to provide evidence of consistent, positive associations between short-term $PM_{2.5}$ and total mortality, across studies that used different approaches to control for the potential confounding effects of weather (e.g., temperature). In addition, there was evidence of biological plausibility for cause-specific mortality and ultimately total mortality as demonstrated by the consistent and coherent evidence across scientific disciplines for cardiovascular morbidity, particularly ischemic events and HF (2019 PM ISA, Chapter 6), and respiratory morbidity, with the strongest evidence coming from studies of exacerbations of COPD and asthma (2019 PM ISA, Chapter 5).

Multicity studies evaluated in the 2019 PM ISA added to the body of evidence evaluated in the 2009 PM ISA and continued to support a positive association between short-term $PM_{2.5}$ exposure and total mortality with percentage increases in mortality ranging from 0.19% to 2.80% at lags of 0 to 1 day in studies in which mean 24-hour avg concentrations were primarily < 20 $\mu g/m^3$ (2019 PM ISA,

Figure 11-1; Table 11-1).[12] The positive associations observed across studies reflected traditional analyses using ambient monitors as well as analyses conducted in both urban and rural locations that used new exposure assignment techniques and relied on multiple sources of $PM_{2.5}$ data (e.g., ambient monitors, statistical models, and satellite data). Whereas the analysis of potential copollutant confounding was limited to single-city studies and studies of PM_{10} in the 2009 PM ISA, recent multicity studies conducted in Europe and Asia indicated that $PM_{2.5}$-mortality associations were relatively unchanged in copollutant models with gaseous pollutants and $PM_{10-2.5}$ (2019 PM ISA, Section 11.1.4). These results from copollutant models further supported an independent effect of $PM_{2.5}$ on mortality. The associations reported for total mortality were also supported by analyses demonstrating increases in cause-specific mortality, specifically for cardiovascular and respiratory mortality which comprise ~33% and ~9%, respectively, of total mortality [NHLBI (2017); 2019 PM ISA, Figure 11-2]. The consistent and coherent evidence across scientific disciplines for cardiovascular morbidity, particularly ischemic events and HF (2019 PM ISA, Chapter 6), and to a lesser degree for respiratory morbidity, with the strongest evidence for exacerbations of COPD and asthma (2019 PM ISA, Chapter 5), provided biological plausibility for cause-specific mortality and ultimately total mortality. The relationship between short-term $PM_{2.5}$ exposure and total mortality was additionally supported by analyses of the concentration-response (C-R) relationship. Although alternatives to linearity have not been systematically evaluated, mortality studies evaluated in the 2019 PM ISA continued to support a linear, no-threshold C-R relationship (2019 PM ISA, Section 11.1.10).

2.1.1.5.2.   Mortality Associated with Long-Term PM2.5 Exposure

Strong epidemiologic evidence from cohorts in the U.S., Canada, and Europe evaluated in the 2019 PM ISA, as well as in previous assessments, continued to support the conclusion of the 2009 PM ISA that there is a *causal relationship* between long-term $PM_{2.5}$ exposure and total mortality (Table 2-2). This conclusion was based on the evaluation of multiple cohorts that continued to provide evidence of consistent, positive associations, across studies that controlled for a range of individual- and ecological covariates, such as smoking status and SES. Additional evidence indicated coherence of effects across scientific disciplines for cardiovascular and respiratory morbidity and metabolic disease, which provided biological plausibility for cause-specific mortality and supported a *causal relationship* with total mortality.

Additional reanalyses and extensions of the American Cancer Society (ACS) and Harvard Six Cities (HSC) cohorts as well as new cohorts consisting of Medicare participants, people that live in Canada, or people employed in a specific job (e.g., teacher, nurse) provided further evidence of positive associations between long-term $PM_{2.5}$ exposure and total mortality, particularly in areas with annual mean

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[12]Throughout this Supplement, as detailed in the Preface of the 2019 PM ISA (Section P.3.2.2), risk estimates from epidemiologic studies examining short-term exposures are for a 10 μg/m³ increase in 24-hour avg $PM_{2.5}$ concentrations and long-term exposures are for a 5 μg/m³ increase in annual concentrations, unless otherwise noted.

concentrations < 20 µg/m^3, and in some cases below 12 µg/m^3 (2019 PM ISA, Figure 11-17 and Figure 11-18). Across studies, positive associations were consistently observed regardless of the exposure assignment approach employed, with some studies relying on ambient monitors while others using modeled or remote sensing data or hybrid methods that combine two or more data sources. Recent studies have conducted analyses to examine potential copollutant confounding and indicated that associations between long-term PM$_{2.5}$ exposure and total mortality are relatively unchanged in copollutant models, particularly for O$_3$, with fewer studies examining NO$_2$, and PM$_{10–2.5}$ (2019 PM ISA, Section 11.2.3; Figure 11-20, Figure 11-21). The evidence for total mortality was further supported by analyses of cause-specific mortality, which reported positive associations with cardiovascular, respiratory, and lung cancer mortality. Biological plausibility for mortality due to long-term PM$_{2.5}$ exposure was provided by the coherence of effects across scientific disciplines for cardiovascular morbidity, particularly for CHD, stroke, and atherosclerosis, and for respiratory morbidity, particularly for the development of COPD. Recent studies extensively examined the C-R relationship between long-term PM$_{2.5}$ exposure and total mortality, specifically in several U.S. and Canadian cohorts, and collectively continued to support a linear, no-threshold C-R relationship (2019 PM ISA, Section 11.2.4; Table 11-7).

A series of studies evaluated in the 2019 PM ISA, examined the relationship between long-term exposure to PM$_{2.5}$ and mortality by examining the temporal trends in PM$_{2.5}$ concentrations to test the hypothesis that decreases in PM$_{2.5}$ concentrations are associated with increases in life expectancy (2019 PM ISA, Section 11.2.2.5). These studies reported that decreases in long-term PM$_{2.5}$ concentrations were associated with an increase in life expectancy across the U.S. for the multiple time periods examined.

Table 2-2   **Key evidence contributing to *causal* and *likely to be causal* causality determinations for PM$_{2.5}$ exposure and health effects evaluated in the 2019 Integrated Science Assessment for Particulate Matter.**

Key Evidence in 2019 PM ISA	Health Effect Category[a] and Causality Determination	PM$_{2.5}$ Concentrations Associated with Effects
Respiratory Effects and Short-Term PM$_{2.5}$ Exposure (2019 PM ISA, Section 5.1): Likely to Be Causal Relationship *No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.*		
Section 5.1.12 Table 5-18	Epidemiologic evidence, consisting mainly of ED visits and hospital admissions, strongly supported a relationship with asthma exacerbation, COPD exacerbation, and combinations of respiratory-related diseases. Evidence for associations with respiratory symptoms and medication use are coherent with other findings for asthma and COPD exacerbation. Some epidemiologic studies examined copollutant confounding and reported that results are robust in models with gaseous pollutants (i.e., O$_3$, NO$_2$, SO$_2$, and with more limited evidence for CO) and other particle sizes (i.e., PM$_{10-2.5}$), especially for asthma exacerbation, combinations of respiratory-related ED visits and hospital admissions, and respiratory mortality. There was a large body of experimental evidence demonstrating respiratory effects due to short-term PM$_{2.5}$ exposure. These experimental studies provided evidence for biologically plausible pathways by which PM$_{2.5}$ exposure could cause a respiratory effect. Specifically, animal toxicological studies provided biological plausibility for asthma exacerbation, COPD exacerbation, and respiratory infection with some evidence of an independent effect of PM$_{2.5}$ on respiratory endpoints. Controlled human exposure studies provided minimal evidence of respiratory effects such as altered lung function and pulmonary inflammation. Consistent positive associations with respiratory mortality provide evidence of a continuum of effects.	Mean ambient concentrations from epidemiologic studies for: *Hospital admissions and ED visits for asthma, COPD, respiratory infections, and combinations of respiratory-related diseases:* U.S. and Canada: 4.7−24. 6 µg/m³ Europe: 8.8−27.7 µg/m³ Asia: 11.8−69.9 µg/m³ *Respiratory mortality:* U.S. and Canada: 7.9−19.9 µg/m³ Europe: 8.0−27.7 µg/m³ Asia: 11.8−69.9 µg/m³ Concentrations from animal toxicological studies for: *Allergic airway disease:* 442−596 µg/m³ *COPD:* 171−1,200 µg/m³ *Altered host defense:* 100−350 µg/m³

Table 2-2 (Continued): Key evidence contributing to *causal* and *likely* to be causal causality determinations for PM$_{2.5}$ exposure and health effects evaluated in the 2019 Integrated Science Assessment for Particulate Matter.

Key Evidence in 2019 PM ISA	Health Effect Category[a] and Causality Determination	PM$_{2.5}$ Concentrations Associated with Effects
Respiratory Effects and Long-Term PM$_{2.5}$ Exposure (2019 PM ISA, Section 5.2): Likely to Be Causal Relationship *No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.*		
Section 5.2.13 Table 5-27	Epidemiologic evidence strongly supported a relationship with decrements in lung function growth in children. Additional epidemiologic evidence supported a relationship with asthma development in children, increased bronchitic symptoms in children with asthma, acceleration of lung function decline in adults, and respiratory mortality, including cause-specific respiratory mortality for COPD and respiratory infection. Some epidemiologic studies examined copollutant confounding and reported that results are robust in models with O$_3$, NO$_2$, and CO, especially for respiratory mortality. There was limited experimental evidence for respiratory effects from long-term PM$_{2.5}$ exposure. However, animal toxicological studies provided biological plausibility for decrements in lung function and asthma development in children, and they reduced the uncertainty regarding the independent effect of PM$_{2.5}$ for these endpoints. Animal toxicological studies also provided evidence for a wide variety of other subclinical effects, such as oxidative stress, inflammation, and morphologic changes. Epidemiologic studies examining the effects of declining PM$_{2.5}$ concentrations strengthened the relationship between long-term PM$_{2.5}$ exposure and respiratory health by demonstrating improvements in lung function growth and reduced bronchitic symptoms in children and improved lung function in adults as a result of lower PM$_{2.5}$ concentrations. However, these studies have a limited examination of copollutant confounding, which was a notable uncertainty because concentrations of other pollutants have also declined.	Mean ambient concentrations from epidemiologic studies for: *Decrement in lung function growth:* 6−28 µg/m^3 *Asthma development in children:* 5.2−16.5 µg/m^3 *Bronchitic symptoms in children with asthma:* 9.9−13.8 µg/m^3 *Accelerated lung function decline in adults:* 9.5−17.8 µg/m^3 *Respiratory mortality:* 6.3−23.6 µg/m^3 Concentrations from animal toxicological studies for: *Impaired lung development:* 16.8 µg/m³ *Development of allergic airway disease:* 100 µg/m³

Table 2-2 (Continued): Key evidence contributing to *causal* and *likely* to be causal causality determinations for PM$_{2.5}$ exposure and health effects evaluated in the 2019 Integrated Science Assessment for Particulate Matter.

Key Evidence in 2019 PM ISA	Health Effect Category[a] and Causality Determination	PM$_{2.5}$ Concentrations Associated with Effects
Cardiovascular Effects and Short-Term PM$_{2.5}$ Exposure (2019 PM ISA, Section 6.1): Causal Relationship		
No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.		
Section 6.1.16 Table 6-34	There was strong evidence for coherence of effects across scientific disciplines and biological plausibility for a range of cardiovascular effects in response to short-term PM$_{2.5}$ exposure. Consistent epidemiologic evidence from multiple studies at relevant PM$_{2.5}$ concentrations provided evidence of increases in ED visits and hospital admissions for IHD and HF, as well as cardiovascular mortality in multicity studies conducted in the U.S., Canada, Europe, and Asia. These associations remained positive, but in some cases were reduced with larger uncertainty estimates, in copollutant models with gaseous pollutants. Controlled human exposure studies provided coherence and consistent evidence for changes in various measures of endothelial dysfunction and generally consistent evidence of changes in BP. These controlled human exposure studies were consistent with animal toxicological studies also demonstrating endothelial dysfunction, as well as changes in BP and the renin-angiotensin system. In addition, animal toxicological studies demonstrating that short-term PM$_{2.5}$ exposure results in decreased cardiac contractility and left ventricular pressure were coherent with epidemiologic studies reporting associations between short-term PM$_{2.5}$ exposure and HF.	Mean ambient concentrations from epidemiologic studies for: *IHD:* 5.8−18.6 µg/m³ *HF:* 5.8−18.0 µg/m³ Concentrations from controlled human exposure studies: 24−325 µg/m³ for 2 h Concentrations from animal toxicological studies: 178−190 µg/m³

Table 2-2 (Continued): Key evidence contributing to *causal* and *likely* to be causal causality determinations for PM$_{2.5}$ exposure and health effects evaluated in the 2019 Integrated Science Assessment for Particulate Matter.

Key Evidence in 2019 PM ISA	Health Effect Category[a] and Causality Determination	PM$_{2.5}$ Concentrations Associated with Effects
Cardiovascular Effects and Long-Term PM$_{2.5}$ Exposure (2019 PM ISA, Section 6.2): Causal Relationship		
No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.		
Section 6.2.18 Table 6-54	Multiple epidemiologic studies continued to provide evidence of consistent, positive associations between long-term PM$_{2.5}$ exposure and cardiovascular mortality at lower ambient concentrations. The cardiovascular mortality associations were observed across different exposure assignment and statistical methods and were relatively unchanged in copollutant models with both gaseous (i.e., O$_3$, NO$_2$, SO$_2$) and particulate (i.e., PM$_{10-2.5}$) pollutants. The evidence for cardiovascular mortality was supported by a smaller body of epidemiologic studies that further explored associations between long-term PM$_{2.5}$ exposure and cardiovascular morbidity. These studies reported some evidence for increased risk of PM$_{2.5}$-related MI and stroke, specifically in individuals with a preexisting cardiovascular disease or diabetes. Recent epidemiologic studies also presented evidence for an effect of long-term PM$_{2.5}$ exposure on subclinical features of cardiovascular morbidity, particularly progression of atherosclerosis as reflected by associations with CAC, with more limited evidence for other measures, such as cIMT. Key evidence from animal toxicological studies included consistent evidence for changes in BP, as well as some evidence for decreases in measures of heart function (e.g., contractility and cardiac output) and cardiac remodeling. Moreover, as in the previous review, there was also some additional evidence for atherosclerotic plaque progression in a genetically susceptible mouse model.	Mean ambient concentrations from epidemiologic studies for: *Cardiovascular mortality*: 4.1–17.9 µg/m^3 *Coronary events*: 13.4 µg/m^3 *CAC*: 14.2 µg/m^3 *CHD and stroke (in those with preexisting disease)*: 13.4–23.9 µg/m^3 Concentrations from animal toxicological studies for: *BP*: 85–375 µg/m^3 (up to 15 weeks)

Table 2-2 (Continued): Key evidence contributing to *causal* and *likely* to be causal causality determinations for PM$_{2.5}$ exposure and health effects evaluated in the 2019 Integrated Science Assessment for Particulate Matter.

Key Evidence in 2019 PM ISA	Health Effect Category[a] and Causality Determination	PM$_{2.5}$ Concentrations Associated with Effects
Nervous System Effects and Long-Term PM$_{2.5}$ Exposure (2019 PM ISA, Section 8.2): Likely to Be Causal Relationship		
Not Evaluated in the 2009 PM ISA; New Evidence Showing Brain Inflammation and Oxidative Stress, Neurodegeneration, Cognitive Effects, and Neurodevelopmental Effects.		
Section 8.2.9 Table 8-20	There was evidence that long-term exposure to PM$_{2.5}$ can modulate the autonomic nervous system leading to downstream consequences, including cardiovascular effects (2019 PM ISA, Section 6.2.1). A second pathway involving neuroinflammation and morphologic changes in the brain indicative of neurodegeneration is well substantiated and coherent across animal toxicological and epidemiologic studies. This combination of evidence supported PM$_{2.5}$-related reductions in brain volume and cognitive effects in older adults. The evidence relating to Parkinson's disease, and neurodevelopmental effects was more limited. Consideration of copollutant confounding was generally lacking in the epidemiologic studies, but the uncertainty in interpreting the study findings was partly addressed by the direct evidence of effects provided by animal toxicological studies.	Mean annual concentrations from epidemiologic studies for: *Brain volume:* 11.1–12.2 µg/m^3 *Cognition:* 8.5 (5-yr avg)–14.9 µg/m^3 *Autism:* 14.0–19.6 µg/m^3 Concentrations from animal toxicological studies for: *Brain inflammation/oxidative stress:* 65.7–441.7 µg/m^3 *Neurodegenerative changes:* 94.4 µg/m^3 *Neurodevelopment:* 92.7 µg/m^3

Table 2-2 (Continued): Key evidence contributing to *causal* and *likely* to be causal causality determinations for PM$_{2.5}$ exposure and health effects evaluated in the 2019 Integrated Science Assessment for Particulate Matter.

Key Evidence in 2019 PM ISA	Health Effect Category[a] and Causality Determination	PM$_{2.5}$ Concentrations Associated with Effects
Cancer and Long-Term PM$_{2.5}$ Exposure (2019 PM ISA, Section 10.2): Likely to Be Causal Relationship		
Change in Causality Determination from the 2009 PM ISA (Suggestive of a Causal Relationship) Due to Increased Evidence of Genotoxicity, Carcinogenicity, and Epigenetic Effects for PM$_{2.5}$ and Lung Cancer Incidence and Mortality.		
Section 10.2.7 Table 10-8	Primarily positive associations from multiple epidemiologic studies reported increases in the risk of lung cancer incidence and mortality. This evidence was supported by analyses focusing on never smokers and limited evidence of associations with histological subtypes of lung cancer found in never smokers. Across studies that examined lung cancer incidence and mortality, potential confounding by smoking status and exposure to SHS was adequately controlled. A limited number of studies examined potential copollutant confounding, but associations were relatively unchanged in models with O$_3$ with more limited assessment of other gaseous pollutants and particle size fractions. Experimental and epidemiologic studies provided evidence for a relationship between PM$_{2.5}$ exposure and genotoxicity, epigenetic effects, and carcinogenic potential. Uncertainties exist due to the lack of consistency in specific cancer-related biomarkers associated with PM$_{2.5}$ exposure across both experimental and epidemiologic studies; however, PM$_{2.5}$ exhibits several characteristics of carcinogens, which provided biological plausibility for PM$_{2.5}$ exposure contributing to cancer development. Additionally, there was limited evidence of cancer occurring in other organ systems, but there was some evidence that PM$_{2.5}$ exposure may detrimentally affect survival from any type of cancer.	Mean annual concentrations from epidemiologic studies for: *Lung cancer incidence and mortality*: U.S. and Canada: 6.3−23.6 µg/m^3 Europe: 6.6−31.0 µg/m^3 Asia: 33.7 µg/m^3 Concentrations from animal toxicological studies for: *Carcinogenic potential:* 17.66 µg/m^3

Table 2-2 (Continued): Key evidence contributing to *causal* and *likely* to be causal causality determinations for PM$_{2.5}$ exposure and health effects evaluated in the 2019 Integrated Science Assessment for Particulate Matter.

Key Evidence in 2019 PM ISA	Health Effect Category[a] and Causality Determination	PM$_{2.5}$ Concentrations Associated with Effects
Total Mortality and Short-Term PM$_{2.5}$ Exposure (2019 PM ISA, Section 11.1): Causal Relationship		
No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.		
Section 11.1.12 Table 11-4	There was consistent epidemiologic evidence from multiple multicity studies conducted in the U.S., Canada, Europe, and Asia for increases in total (nonaccidental) mortality at ambient concentrations, often below 20 µg/m^3. The associations observed were relatively unchanged in copollutant models with gaseous pollutants and PM$_{10-2.5}$, which was consistent with copollutant analyses for cardiovascular and respiratory mortality, but copollutant analyses were limited to studies conducted in Europe and Asia. Biological plausibility for the epidemiologic evidence for total mortality was provided by the strong cardiovascular morbidity evidence, particularly for ischemic events and HF, while support for biological plausibility was more limited from the respiratory morbidity evidence, with the strongest evidence for exacerbations of COPD and asthma. Although alternatives to linearity have not been systematically evaluated, recent mortality studies continued to support a linear, no-threshold C-R relationship.	Mean 24-h avg concentrations from epidemiologic studies for: *Total mortality*: U.S. and Canada: 4.37−17.97 µg/m^3 Europe: 13−27.7 µg/m^3 Asia: 11.8−69.9 µg/m^3

Table 2-2 (Continued): Key evidence contributing to *causal* and *likely* to be causal causality determinations for PM$_{2.5}$ exposure and health effects evaluated in the 2019 Integrated Science Assessment for Particulate Matter.

Key Evidence in 2019 PM ISA	Health Effect Category[a] and Causality Determination	PM$_{2.5}$ Concentrations Associated with Effects

Total Mortality and Long-Term PM$_{2.5}$ Exposure (2019 PM ISA, Section 11.2): Causal Relationship

No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.

Section 11.2.7 Table 11-8	There was consistent epidemiologic evidence from multiple studies reporting increases in the risk of total (nonaccidental) mortality from extended follow-ups of the ACS cohort and HSC cohort, as well as multiple studies focusing on a Medicare cohort, Canadian cohorts, and North American employment cohorts. The consistent increases in total mortality were observed across different exposure metrics based on ambient measurements, models, remote sensing, or hybrid methods that combine two or more of these methods, providing additional support for the mortality associations due to long-term PM$_{2.5}$ exposure reported in the 2009 PM ISA that relied on exposure metrics from ambient monitors. The consistent epidemiologic evidence for total mortality was supported by positive associations for cardiovascular, respiratory, and lung cancer mortality. Biological plausibility for total mortality was provided by the strong cardiovascular morbidity evidence, particularly for CHD, stroke, and atherosclerosis, while there is more limited evidence for biological plausibility from the respiratory morbidity evidence, with some evidence for development of COPD. Extensive epidemiologic evidence provides additional support for a linear, no-threshold C-R relationship. A series of studies demonstrated that decreases in long-term PM$_{2.5}$ concentrations were associated with an increase in life expectancy across the U.S. for multiple time periods examined.	Mean annual concentrations from epidemiologic studies for: *Total mortality*: ACS/HSC cohorts: 11.4−23.6 μg/m^3 Medicare cohort: 8.12−12.0 μg/m^3 Canadian cohorts: 8.7−9.1 μg/m^3 Employment cohorts: 12.7−17.0 μg/m^3

ACS = American Cancer Society; avg = average; BP = blood pressure; CAC = coronary artery calcification; CHD = coronary heart disease; cIMT = carotid intima-media thickness; CO = carbon monoxide; COPD = chronic obstructive pulmonary disease; C-R = concentration-response; h = hour; HF = high frequency; HSC = Harvard Six Cities; IHD = ischemic heart disease; μg/m^3 = micrograms per cubic meter; MI = myocardial infarction; NO$_2$ = nitrogen dioxide; O$_3$ = ozone; PM$_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm; PM$_{10-2.5}$ = particulate matter with a nominal mean aerodynamic diameter greater than 2.5 μm and less than or equal to 10 μm; SHS = second-hand smoke; SO$_2$ = sulfur dioxide.

[a]A large spectrum of outcomes is evaluated as part of a broad health effect category including physiological measures (e.g., airway responsiveness, lung function), clinical outcomes (e.g., respiratory symptoms, hospital admissions), and cause-specific mortality. Total mortality includes all nonaccidental causes of mortality and is informed by the nature of the evidence for the spectrum of morbidity effects (e.g., respiratory, cardiovascular) that can lead to mortality. The sections and tables referenced in the 2019 PM ISA include a detailed discussion of the available evidence that informed the causality determinations.

2.2. Policy-Relevant Considerations

In the process of evaluating the current state of the science with respect to the effect of short- and long-term PM exposure on health, studies were identified and evaluated within the 2019 PM ISA that conducted analyses focused on addressing some of the main policy-relevant questions of this review, as detailed in the *Integrated Review Plan for the National Ambient Air Quality Standards for Particulate Matter* (U.S. EPA, 2016), such as:

- Is there new evidence aimed at disentangling the effect of PM from the complex air pollution mixture to inform a direct effect of PM on health, specifically the assessment of potential copollutant confounding?

- Is there new evidence to inform the current indicators (i.e., $PM_{2.5}$ for fine particles and PM_{10} for thoracic coarse particles), averaging times (i.e., 24-hour avg, annual average), and levels of the PM NAAQS?

- Is there new evidence on the shape of the C-R relationship and whether a threshold exists between PM exposure and various health outcomes (e.g., mortality, hospital admissions), especially for concentrations near or below the levels of the current PM NAAQS?

- Is there new evidence that individual PM component(s) or source(s) (e.g., industrial facilities, roads, atmospheric formation), are more strongly associated with health effects than PM mass, particularly for health effects for which there is sufficient evidence of a strong relationship (e.g., cardiovascular effects, mortality) with PM exposure?

- Is there new evidence indicating that specific populations or lifestages are at increased risk of a PM-related health effect compared with a referent population?

The following sections summarize the evidence that can inform consideration of these policy-relevant questions, specifically: potential copollutant confounding (Section 2.2.1), timing of effects (Section 2.2.2), C-R relationship (Section 2.2.3), PM components and sources (Section 2.2.4), and populations potentially at increased risk of a PM-related health effect (Section 2.2.5).

2.2.1.   Potential Copollutant Confounding

Studies evaluated in the 2019 PM ISA further examined the potential confounding effects of copollutants, both gaseous and particulate, on the relationship between short- and long-term $PM_{2.5}$ exposure and health effects. These studies built upon the evidence detailed in the 2009 PM ISA and continued to provide evidence indicating that associations with $PM_{2.5}$ are relatively unchanged in copollutant models. Evidence from epidemiologic studies, in combination with experimental studies detailed in multiple chapters of the 2019 PM ISA (i.e., "Respiratory Effects"—Chapter 5 and "Cardiovascular Effects"—Chapter 6 within the 2019 PM ISA) that examined exposure to PM

(e.g., CAPs, resuspended PM, and whole mixtures in the presence and absence of a particle trap), demonstrate a direct effect of PM on health.

2.2.1.1.   Short-Term PM$_{2.5}$ Exposure

Building upon the studies evaluated in the 2009 PM ISA, epidemiologic studies evaluated in the 2019 PM ISA have further examined whether copollutants confound associations between short-term PM$_{2.5}$ exposure and respiratory and cardiovascular effects and mortality. These studies continued to demonstrate that PM$_{2.5}$-associations are relatively unchanged in copollutant models with both gaseous (i.e., O$_3$, NO$_2$, SO$_2$, and CO) and particulate (i.e., PM$_{10-2.5}$) pollutants.

The examination of potential copollutant confounding on the relationship between short-term PM$_{2.5}$ exposure and respiratory effects has been assessed most extensively through studies examining respiratory-related ED visits and hospital admissions, particularly for asthma, with more limited assessments of COPD and respiratory infection, and studies examining respiratory mortality (Section 5.1.10.1). Correlations between PM$_{2.5}$ and gaseous and particulate pollutants varied across studies, with low to moderate correlations (i.e., $r < 0.7$) observed for NO$_2$, SO$_2$, CO, and PM$_{10-2.5}$, and correlations spanning from low to high for O$_3$. Across the studies that assessed copollutant confounding, O$_3$ was most examined, followed by NO$_2$ and PM$_{2.5}$. Within these studies results were relatively unchanged in copollutant models. Although fewer studies focused on SO$_2$ and CO, the results from copollutant analyses were consistent with studies evaluated in the 2009 PM ISA, indicating that results are relatively unchanged in copollutant models. Studies evaluated in the 2019 PM ISA that examined PM$_{10-2.5}$ further expanded upon the initial results detailed in the 2009 PM ISA, and although results are consistent with observations from analyses of gaseous pollutants, there is greater uncertainty in these results due to the different methods employed across studies to estimate PM$_{10-2.5}$ concentrations.

For cardiovascular effects, moderate to strong correlations were reported for NO$_2$ and CO, with low to moderate correlations for O$_3$, SO$_2$, and PM$_{10-2.5}$. Across studies of various cardiovascular-related ED visits and hospital admissions and cardiovascular mortality, results were relatively unchanged in copollutant models, but there were some instances of attenuation of the PM$_{2.5}$ association in models with NO$_2$ and CO (2019 PM ISA, Section 6.1.14.1). Overall, there was no observed difference in the trend or pattern of copollutant model results across cardiovascular endpoints (e.g., aggregate CVD endpoints, IHD, HF, cardiovascular mortality). However, the few instances of attenuation were with traffic-related pollutants (i.e., NO$_2$, CO), which generally had higher correlations with PM$_{2.5}$ than the other copollutants. As a result, it was difficult to distinguish whether the instances of observed attenuation in PM$_{2.5}$ associations were due to confounding or collinearity with other pollutants.

Most epidemiologic studies evaluated in the 2019 PM ISA that examined the potential confounding effects of copollutants focused on respiratory and cardiovascular effects; only a few focused on mortality (2019 PM ISA, Section 11.1.4). Recent multicity studies conducted in Europe and Asia

supported the results from single- and multicity studies examined in the 2004 PM AQCD and 2009 PM ISA that reported limited evidence of confounding by copollutants. Across studies that examined both gaseous and particulate (i.e., $PM_{10–2.5}$) pollutants, low to moderate correlations were reported with $PM_{2.5}$. Associations with $PM_{2.5}$ were relatively unchanged in copollutant models across the various study locations examined.

In addition to conducting traditional copollutant analyses, epidemiologic studies of respiratory (2019 PM ISA, Section 5.1.10.1.1) and cardiovascular (2019 PM ISA, Section 6.1.14.1.1) effects have also examined the role of PM within the broader air pollution mixture. These studies do not inform whether PM is independently associated with a respiratory effect, but they can assess whether days with higher $PM_{2.5}$ concentrations are more closely related to health effects. Studies of respiratory effects demonstrated that days when the air pollution mixture has high $PM_{2.5}$ concentrations often represented the days with the largest associations (in terms of magnitude) with a respiratory effect. Additionally, results indicated that risk estimates for a mixture were often similar, but in some cases larger, than those reported for $PM_{2.5}$ alone. However, for cardiovascular effects in general, the evidence neither consistently nor coherently indicated a stronger or weaker effect of combined exposure to $PM_{2.5}$ and another pollutant compared with exposure to $PM_{2.5}$ and other pollutants alone.

2.2.1.2.   Long-Term PM$_{2.5}$ Exposure

Epidemiologic studies focusing on long-term $PM_{2.5}$ exposure and health effects have traditionally provided a more limited assessment of the potential confounding effects of copollutants on $PM_{2.5}$ associations. Studies evaluated in the 2019 PM ISA that provided an assessment of copollutant confounding directly addressed a previously identified uncertainty in the scientific evidence.

Across the health effects evaluated within the 2019 PM ISA, relatively few studies examined the potential confounding effects of copollutants on the relationship between long-term $PM_{2.5}$ exposure and respiratory (2019 PM ISA, Section 5.2.13), cardiovascular (2019 PM ISA, Section 6.2.18), and cancer (2019 PM ISA, Section 10.2.7), with a general lack of studies assessing the role of copollutant confounding on observed associations with nervous system effects (2019 PM ISA, Section 8.2.9). These studies often did not examine the full suite of gaseous pollutants but tended to focus on traffic-related pollutants (i.e., NO_2, NO_X, and CO) and O_3, with some studies also examining $PM_{10–2.5}$. Across studies, low to moderate correlations (i.e., $r < 0.7$) were often observed between copollutants and $PM_{2.5}$. Collectively, studies that examined the potential confounding effects of copollutants on the $PM_{2.5}$ association with respiratory (i.e., lung function and asthma development) and cardiovascular effects (i.e., cardiovascular mortality), along with lung cancer incidence and mortality, reported associations that were relatively unchanged in copollutant models, but these assessments were conducted in a limited number of studies.

Several studies of long-term $PM_{2.5}$ exposure and mortality examined potential copollutant confounding. Within studies that examined the potential confounding effects of copollutants on the relationship between long-term $PM_{2.5}$ exposure and mortality, the most extensive analyses occurred for O_3, with a limited number of studies examining NO_2, SO_2, $PM_{10-2.5}$, and benzene. Studies that examined O_3 reported correlations that were generally moderate (ranging from $r = 0.49$ to 0.73), with a few studies reporting weak correlations ($r < 0.4$). Overall, associations remained relatively unchanged in copollutant models for total (nonaccidental) mortality, cardiovascular, and respiratory mortality (2019 PM ISA, Figure 11-18). Studies focusing on copollutant models with NO_2, $PM_{10-2.5}$, SO_2, and benzene were examined in individual studies, and across these studies the $PM_{2.5}$-mortality association was relatively unchanged (2019 PM ISA, Figure 11-19).

2.2.2.   Timing of Effects

An important question to address when evaluating the scientific evidence demonstrating health effects due to short-term $PM_{2.5}$ exposure is the timing of observed effects. Studies have attempted to address this question through two primary avenues: (1) examining various averaging times of the exposure metric used to represent short-term $PM_{2.5}$ exposure to determine whether $PM_{2.5}$ concentrations averaged over time periods other than 24 hours are more closely associated with health effects and (2) assessing whether the relationship between exposure and effect is biologically plausible by examining the lag days over which associations are observed.

2.2.2.1.   Averaging Time

Most epidemiologic studies evaluated in the 2019 PM ISA that examined the relationship between short-term $PM_{2.5}$ exposures and health effects relied primarily on an exposure metric averaged over 24-hours. Some recent studies, focusing on respiratory and cardiovascular effects and mortality, have examined whether there is evidence that subdaily exposure metrics are more closely related to health effects than the traditional 24-hour avg metric.

Epidemiologic studies that examined both respiratory-related ED visits and hospital admissions, as well as subclinical markers of respiratory effects, explored associations with subdaily exposure metrics (2019 PM ISA, Section 5.1.10.5). In studies of respiratory-related ED visits and hospital admissions, positive associations were not consistently observed with subdaily exposure metrics, and often there was no information on spatiotemporal variability of the subdaily metrics. Additionally, in a study that examined multiple subdaily averaging times and compared them with the 24-hour avg exposure metric, there was no difference in associations across metrics, but this result was limited to a single study location. Panel studies also examined subdaily exposure metrics through personal monitoring, but

associations were not consistently observed at shorter averaging times for markers of pulmonary inflammation and changes in lung function.

A more limited number of studies examined subdaily exposure metrics and cardiovascular effects (2019 PM ISA, Section 6.1.14.3). Studies of ST elevation, myocardial infarction, out-of-hospital cardiac arrest, and cerebrovascular disease ED visits and hospital admissions reported positive associations with subdaily exposure metrics, but the magnitude of the association tended to be larger when averaging over multiple hours up to 1 day (i.e., 24-hour avg). These studies provided evidence that continues to support the use of a 24-hour avg exposure metric.

A few studies examined subdaily $PM_{2.5}$ exposure metrics and associations with mortality, focusing on comparisons between the 24-hour avg and an hourly peak exposure metric (2019 PM ISA, Section 11.1.8.2). In these studies, positive associations were reported for both the 24-hour avg and hourly peak exposure metric, with the association often slightly larger in magnitude for the 24-hour avg metric. Collectively, the available evidence did not indicate that subdaily averaging periods for $PM_{2.5}$ were more closely associated with health effects than the 24-hour avg exposure metric.

2.2.2.2.   Lag Structure of Associations

Often epidemiologic studies examined associations between short-term $PM_{2.5}$ exposure and health effects over a series of single-day lags, multiday lags, or by selecting lags a priori. Studies evaluated in the 2019 PM ISA have expanded the assessment of the timing of effects by systematically examining lag days by focusing on whether there is evidence of an immediate (e.g., lag 0−1 days), delayed (e.g., lag 2−5 days), or prolonged (e.g., lag 0−5 days) effect of PM on health.

Epidemiologic studies of respiratory effects have primarily focused on examining the lag structure of associations for respiratory-related ED visits and hospital admissions, with most studies examining asthma exacerbation with a more limited assessment for COPD exacerbation and respiratory infection (2019 PM ISA, Section 5.1.10.3). Across the studies that examined asthma, COPD, respiratory infections, and combinations of respiratory-related diseases, the strongest association reported, in terms of magnitude and precision, was generally within a few days after exposure, but there was some evidence demonstrating the potential for a prolonged effect of $PM_{2.5}$ (i.e., lags ranging from 0 to 5 days). Recent studies of respiratory mortality provided additional insight on the lag structure of associations for respiratory-related effects due to short-term $PM_{2.5}$ exposure. Studies of respiratory mortality tended to support more immediate $PM_{2.5}$ effects (i.e., lags of 0 to 2 days), but with initial evidence of stronger associations, in terms of magnitude and precision, at lags of 0−5 days. Collectively, the studies of respiratory morbidity and mortality that conducted systematic evaluations of $PM_{2.5}$ associations across a range of lags provided evidence of effects within the range of 0−5 days after exposure.

As with respiratory effects, the majority of epidemiologic studies examining the lag structure of associations for cardiovascular effects focused on ED visits and hospital admissions. Studies of ED visits and hospital admissions for IHD, MI, and cardiovascular-related outcomes reported stronger associations for multiday lags, but these effects tended to be in the range of 0−1 or 0−2 days. When examining cerebrovascular disease, there was no evidence of an association at any of the lag days examined; however, when focusing on specific stroke types, particularly ischemic stroke, there was evidence of immediate effects at lags of 0 and 1 day, which was consistent with other cardiovascular outcomes. The immediate effects of $PM_{2.5}$ on cardiovascular morbidity outcomes, specifically those related to ischemic events, were consistent with the lag structure of associations observed in studies of cardiovascular mortality that reported immediate effects (i.e., lag 0−1 day). There was some evidence indicating $PM_{2.5}$-cardviovascular mortality associations with exposures over longer durations, but this was not supported by studies examining single-day lags that encompassed the same number of days.

An evaluation of epidemiologic studies of short-term $PM_{2.5}$ exposure and mortality found that studies either conducted analyses of single-day lags over many days or various iterations of multiday lags (e.g., 0−1, 0−2, 0−3; 2019 PM ISA, Section 11.1.8.1). Across studies, associations were largest in terms of magnitude and precision for total (nonaccidental) mortality at lags of 0 to 1 day, but there was some evidence that associations remained positive at multiday lags up to 0−4 days. The combination of the multi- and single-day lag analyses provided further support of an immediate effect of short-term $PM_{2.5}$ exposure on mortality.

2.2.3.   Concentration-Response Relationship

In assessing the relationship between short- and long-term PM exposure and health effects, an important consideration is whether the relationship is linear across the full range of ambient concentrations and whether a threshold concentration exists below which there is no evidence of an effect. As detailed in the 2004 AQCD and 2009 PM ISA, conducting C-R and threshold analyses is challenging because of the "(1) limited range of available concentration levels (i.e., sparse data at the low and high end); (2) heterogeneity of (at-risk) populations (between cities); and (3) influence of measurement error" (U.S. EPA, 2004). Studies evaluated in the 2019 PM ISA that focused on the shape of the C-R curve expanded upon the health effects evaluated in previous reviews and continued to provide evidence of a linear, no-threshold relationship between both short- and long-term $PM_{2.5}$ exposure and several respiratory and cardiovascular effects, and mortality. Some evidence indicated a steeper slope (i.e., supralinear curve) at lower concentrations for some outcomes (i.e., long-term $PM_{2.5}$ exposure and mortality). Cutpoint analyses that focused on whether risk changed at different concentration ranges provided some evidence of nonlinearity, specifically in the relationship between short-term $PM_{2.5}$ exposure and respiratory-related ED visits and hospital admissions. Although studies evaluated in the 2019 PM ISA have used many different statistical methods to examine the shape of the C-R relationship

and generally provided evidence for a linear, no-threshold relationship, many of these studies have not systematically evaluated alternatives to a linear relationship.

2.2.3.1.   Short-Term Exposure

Epidemiologic studies evaluated in the 2019 PM ISA that examined the C-R relationship between short-term $PM_{2.5}$ exposure and health were limited to studies of respiratory-related ED visits and hospital admissions (2019 PM ISA, Section 5.1.10.6) and mortality (2019 PM ISA, Section 11.1.10). Across studies that examined respiratory effects, different analytical methods have been employed to examine the C-R relationship, either explicitly examining the shape of the C-R curve and whether there was evidence of linearity across the full range of $PM_{2.5}$ concentrations, or through cutpoint analyses that examine whether the risk of a $PM_{2.5}$-related respiratory effect changed within specified ranges of $PM_{2.5}$ concentrations. These studies primarily focused on asthma ED visits and hospital admissions, with some studies examining combinations of respiratory-related ED visits and hospital admissions. Studies that focused on the shape of the C-R curve provided initial evidence of a linear relationship for short-term $PM_{2.5}$ exposure and both respiratory disease and asthma ED visits and hospital admissions, with less certainty at concentrations below 10 $\mu g/m^3$. However, cutpoint analyses provided some initial evidence indicating nonlinearity in the relationship (i.e., larger risk estimates at various quintiles when compared with the lowest quintile) between short-term $PM_{2.5}$ exposure and asthma ED visits and hospital admissions.

Studies that examined the C-R relationship for short-term PM exposure and mortality were initially limited to those focusing on PM_{10}. Recent epidemiologic studies focused on $PM_{2.5}$ and specifically the shape of the C-R curve at the low end of the $PM_{2.5}$ concentration distribution. Evidence from U.S. studies conducted at lower $PM_{2.5}$ concentrations compared with other countries, provided evidence indicating a linear relationship at concentrations as low as 5 $\mu g/m^3$. The observations from C-R analyses were further supported by cutpoint analyses examining associations at different $PM_{2.5}$ concentrations, as well as analyses that reported no evidence of a threshold. Overall, studies evaluated in the 2019 PM ISA focusing on short-term $PM_{2.5}$ exposure and mortality supported a linear, no-threshold relationship at ambient $PM_{2.5}$ concentrations lower than those evaluated in the 2009 PM ISA.

2.2.3.2.   Long-Term Exposure

The most extensive analyses of the C-R relationship between long-term PM exposure and a health effect have generally been for $PM_{2.5}$ and mortality. Recent studies further expanded and provided new insights on the relationship between long-term $PM_{2.5}$ exposure and mortality. In addition, these studies provided initial examinations of the C-R relationship for respiratory and cardiovascular effects, as well as for lung cancer incidence and mortality.

Although the C-R relationship for long-term $PM_{2.5}$ exposure has not been assessed for most health effects, it has been extensively examined in studies of mortality (2019 PM ISA, Section 11.2.4). Across studies, a variety of statistical methods have been used to assess whether there is evidence of deviations in linearity. Studies have also conducted cutpoint analyses that focus on examining risk at specific ambient concentrations (2019 PM ISA, Table 11-7). These studies reported results that generally support a linear, no-threshold relationship for total (nonaccidental) mortality, especially at lower ambient $PM_{2.5}$ concentrations, with confidence in the linear relationship as low as 5−8 $\mu g/m^3$ in some studies. Additionally, there was initial evidence indicating that the slope of the C-R curve may be steeper (supralinear) at lower concentrations for cardiovascular mortality.

Few epidemiologic studies have examined the C-R relationship for long-term $PM_{2.5}$ exposure and respiratory effects (2019 PM ISA, Section 5.2.3.1.2), but the ones that have focused on asthma incidence and childhood wheeze. Studies of asthma incidence that examined the shape of the C-R curve and whether risk changes at different quartiles of $PM_{2.5}$ concentrations did not find any evidence of deviations in linearity and monotonically increasing risk, respectively. In an initial study of childhood wheeze, specifically repeated wheeze events, there was evidence of a linear C-R relationship with confidence in the linear relationship at long-term $PM_{2.5}$ concentrations as low as 10 to 12 $\mu g/m^3$.

A limited number of studies reported initial assessments of the C-R relationship for long-term $PM_{2.5}$ concentrations and cardiovascular effects, specifically IHD incidence, CAC, and hypertension (2019 PM ISA, Section 6.2.16). For IHD incidence, there was evidence of a linear C-R relationship at concentrations below 15 $\mu g/m^3$, which was consistent with the shape of the curve when compared with the full range of $PM_{2.5}$ concentrations. Analyses of the relationship between long-term $PM_{2.5}$ exposure and CAC indicated both linear and nonlinear relationships, while there is preliminary evidence of a linear relationship between long-term $PM_{2.5}$ exposure and incidence of hypertension. A few studies that examined the relationship between long-term $PM_{2.5}$ exposure and lung cancer incidence and mortality also examined the shape of the C-R curve by assessing its linearity and conducting cutpoint and threshold analyses (2019 PM ISA, Section 10.2.5.1.4). These collective assessments provided initial evidence supporting a no-threshold, linear relationship across the range of $PM_{2.5}$ concentrations observed in the U.S., with confidence in a linear relationship as low as 5−10 $\mu g/m^3$ in some studies.

2.2.4.   PM Components and Sources

Building on the initial evaluation conducted in the 2004 PM AQCD, the 2009 PM ISA formally evaluated the relationship between exposures to PM components and sources and health effects. This evaluation found that many components and sources representative of combustion-related activities (e.g., motor vehicle emissions, coal combustion, oil burning, vegetative burning) were associated with a range of health effects. The 2009 PM ISA, therefore, concluded that "many [components] of PM can be

linked with differing health effects and the evidence is not yet sufficient to allow differentiation of those components or sources that are more closely related to specific health outcomes."

Building upon the evaluation of PM sources and components in the 2009 PM ISA, and as detailed in the Preface of the 2019 PM ISA, the 2019 PM ISA systematically evaluated whether specific PM components or sources were more strongly associated with health effects than PM mass by focusing on those studies that: (1) included a composite metric of PM (e.g., mass of $PM_{2.5}$ and/or $PM_{10-2.5}$, or in the case of ultrafine particles [UFP] mass, particle number) and PM components; (2) applied some approach to assess the particle effect (e.g., particle trap) of a mixture; or (3) conducted formal statistical analyses to identify source-based exposures (see 2019 PM ISA, Preface). Overall, these criteria allowed for a thorough evaluation of whether there was evidence that an individual component(s) and/or source(s) was more closely related to health effects than PM mass. Across the health effects categories evaluated in the 2019 PM ISA, most studies that examined PM sources and components focused on $PM_{2.5}$. Thus, the following sections summarize the state of the science on $PM_{2.5}$ components and sources for those health effects categories for which it was concluded within the 2019 PM ISA that there was a *causal* or *likely to be causal relationship*. Details on the $PM_{2.5}$ components and sources evidence relevant to other health effects categories (e.g., Reproductive and Developmental Effects) are covered in the health chapters of the 2019 PM ISA.

Overall, recent studies continued to demonstrate that many $PM_{2.5}$ components and sources were associated with health effects ranging from subclinical (e.g., changes in heart function, such as HRV, or circulating biomarkers) to the more overt (i.e., ED visits, hospital admissions, and mortality). The results of these studies confirmed and further supported the conclusion of the 2009 PM ISA that many $PM_{2.5}$ components and sources are associated with many health effects and that the evidence does not indicate that any one source or component is consistently more strongly related with health effects than $PM_{2.5}$ mass.

2.2.4.1.   Respiratory Effects

The examination of $PM_{2.5}$ components and sources and respiratory effects was limited to epidemiologic studies (2019 PM ISA, Section 5.1.11). Epidemiologic studies that examined the relationship between respiratory health effects and short-term exposure to both $PM_{2.5}$ mass (n = 113) and $PM_{2.5}$ components, primarily focused on the components nitrate (n = 29), sulfate (n = 40), OC (n = 50), and EC/BC (n = 95). Across these studies, the health effects examined range from inflammation and changes in lung function to respiratory-related ED visits and hospital admissions. When examining the pattern of associations for individual $PM_{2.5}$ components with those observed for $PM_{2.5}$ mass, all the components examined (i.e., evaluated in at least three studies) were positively associated with a respiratory effect in at least a few studies (2019 PM ISA, Section 5.1.11.7). For EC/BC, the most extensively examined $PM_{2.5}$ component, many studies reported positive associations, but some studies

also reported results indicating no association, which was consistent with the pattern of associations for $PM_{2.5}$ mass.

A more limited number of studies examined associations between long-term $PM_{2.5}$ components exposure and respiratory effects (2019 PM ISA, Section 5.2.12). Similar to short-term exposure studies, most long-term exposure studies focused on EC/BC and did not observe a pattern of associations with respiratory effects different from that observed for $PM_{2.5}$ mass. Collectively, positive associations were observed in studies examining short- and long-term $PM_{2.5}$ component exposure and respiratory effects, but there was no evidence that any one component was more strongly associated with respiratory effects than $PM_{2.5}$ mass.

Few studies examined the relationship between $PM_{2.5}$ sources and respiratory health effects. Through analyses in which $PM_{2.5}$ components were apportioned into source factors, positive associations were reported for several respiratory effects, particularly asthma exacerbation, and sources representative of combustion-related activities, such as traffic and biomass burning. No studies evaluated in the 2019 PM ISA examined long-term exposure to $PM_{2.5}$ sources and respiratory effects.

2.2.4.2.   Cardiovascular Effects

Both epidemiologic and experimental studies examined the relationship between exposure to $PM_{2.5}$ component and sources and cardiovascular effects (2019 PM ISA, Section 6.1.15). In short-term exposure studies, the epidemiologic evidence focused on studies examining cardiovascular-related ED visits and hospital admissions, with only a few studies examining other cardiovascular effects. Similar to respiratory effects studies, the cardiovascular effects studies that examined both $PM_{2.5}$ mass and components (n = 14) focused most extensively on EC (n = 12), OC (n = 10), sulfate (n = 9), and nitrate (n = 9). Across all components examined, most were positively associated with cardiovascular-related ED visits and hospital admissions in at least one study (2019 PM ISA, Section 6.1.15). Although EC was positively associated with cardiovascular-related ED visits and hospital admissions in many of the studies evaluated, it was not possible to tell whether EC was independently associated or a marker of exposure to $PM_{2.5}$ mass.

Few studies examined long-term exposure to $PM_{2.5}$ components and cardiovascular effects, and those that did were consistent with the long-term exposure and respiratory effects studies that primarily focused on EC/BC (2019 PM ISA, Section 6.2.17). These studies did not provide evidence that any one component was more strongly associated with a cardiovascular effect. Collectively, studies examining short- and long-term $PM_{2.5}$ components exposure continue to support that there is no evidence that any one component is more strongly associated with a cardiovascular effect than $PM_{2.5}$ mass.

Epidemiologic and animal toxicological studies conducted source-based analyses using mathematical methods to apportion $PM_{2.5}$ components into source factors (2019 PM ISA, Section 6.1.15.6

and Section 6.1.15.8). Epidemiologic studies focused on cardiovascular-related ED visits and hospital admissions and reported positive associations with sources representative of combustion-related activities (e.g., industrial combustion, traffic), with more limited evidence for wildfires. Animal toxicological studies, which focused on markers of heart function (e.g., HR, HRV), reported associations with a variety of source categories, but the associations were dependent on the location of the study (i.e., where the $PM_{2.5}$ CAPs were collected). Additional studies focusing on long-term exposures to $PM_{2.5}$ sources were fewer, with epidemiologic studies only examining traffic sources and animal toxicological studies reporting associations between a number of sources and various cardiovascular effects.

2.2.4.3.   Mortality

Epidemiologic studies that examined associations with $PM_{2.5}$ components and sources and mortality have primarily focused on examining short- and long-term exposures to components (2019 PM ISA, Section 11.1.11 and Section 11.2.6). Both short- and long-term exposure studies reported consistent, positive associations with $PM_{2.5}$ mass across all studies that also examined a $PM_{2.5}$ component. Although the respiratory and cardiovascular effects studies focused mainly on EC/BC, the studies of mortality did not examine any one component disproportionately over the others. Of the $PM_{2.5}$ components examined, each were found to be positively associated with mortality in at least a few studies, but overall, one component was not found to be as consistently associated with mortality as $PM_{2.5}$ mass.

Compared with the 2009 PM ISA, in which most epidemiologic studies of mortality conducted formal source apportionment analyses, studies evaluated in the 2019 PM ISA have focused more exclusively on $PM_{2.5}$ components. Of the limited number of studies that examined associations between short- and long-term source exposures and mortality, positive associations were observed for those sources representative of combustion-related activities, including traffic, coal, and vegetative fires.

2.2.5.   Populations and Lifestages at Potentially Increased Risk of a PM-Related Health Effect

An important consideration in evaluating the scientific evidence for PM, and in determining the extent to which the NAAQS provides public health protection, is whether specific populations or lifestages are at increased risk of a PM-related health effect. As detailed in the preceding sections of this chapter and in health effects chapters of the 2019 PM ISA, a large body of evidence shows that health effects related to PM exposure, particularly $PM_{2.5}$ exposure, occur across populations with diverse characteristics (e.g., children, older adults, people with preexisting cardiovascular diseases). Although this larger body of evidence provided information on the causal nature of the relationship between PM exposure and health effects, this section focuses on answering the following question:

Are there specific populations and lifestages at increased risk of a PM-related health effect, compared to a reference population? That is, is the magnitude of effect or exposure greater for some populations or lifestages compared to a reference population, where applicable?

The evaluation of populations and lifestages potentially at increased risk builds off the approach used in the 2009 PM ISA and involved application of a framework detailed in the 2013 O_3 ISA to characterize the evidence informing whether a population or lifestage is at increased risk (U.S. EPA, 2013). The focus of this evaluation was on determining the extent to which specific factors may increase the risk of a PM-related health effect in a population or lifestage relative to a reference population, where applicable. Importantly, this evaluation builds on the conclusions drawn elsewhere in the 2019 PM ISA, taking into consideration the relationship between exposure to PM and health effects. As detailed in the Preamble to the ISAs (U.S. EPA, 2015), the evaluation of the evidence includes (1) epidemiologic studies that conducted stratified analyses, (2) evidence from animal toxicological studies using animal models of disease and epidemiologic or controlled human exposure studies conducted in specific populations (e.g., lung function growth in children, people with mild asthma), (3) information on the dosimetry of PM within the body, and (4) consideration of information on differential exposure to PM within a population or lifestage. Overall, the framework allows for a transparent characterization of the collective body of evidence to draw conclusions on the degree to which the scientific evidence indicates that a specific population or lifestage is at increased risk of a PM-related health effect (2019 PM ISA, Table 12-1).

The causality determinations briefly summarized within this section, which are more fully detailed in the health effects chapters of the 2019 PM ISA, suggest that the strongest evidence indicating an effect of short- and long-term PM exposure on health is for $PM_{2.5}$ and the broad health categories of respiratory and cardiovascular effects, nervous system effects, cancer, and mortality. Thus, the assessment of populations and lifestages potentially at increased risk of a $PM_{2.5}$-related health effect primarily focused on studies that form the basis of these causality determinations that also conducted analyses to inform whether there is differential risk in a specific population or lifestage. In evaluating studies, several factors can influence the ability to observe an association, including, but not limited to, publication bias (i.e., not reporting null findings when examining evidence of differential risk), variability in how indicators or metrics are defined across studies (e.g., socioeconomic status, obesity, age), and variability in the population as a whole, particularly with respect to behavioral differences, biological differences (e.g., obese versus nonobese), and adherence to treatment for preexisting diseases.

Of the factors evaluated (2019 PM ISA, Table 12-3 for a full list), children and race were the only factors for which it was concluded that *"adequate evidence"* was available, indicating that people of a specific lifestage and race are at increased risk of $PM_{2.5}$-related health effects (2019 PM ISA, Section 12.5.1.1 and Section 12.5.4). Although stratified analyses do not indicate a difference in the risk of PM-related health effects between children and adults, there was strong evidence from studies focusing on children that demonstrated health effects only observable in growing children that were attributed to $PM_{2.5}$ exposure. Specifically, epidemiologic studies evaluated in the 2019 PM ISA of long-term $PM_{2.5}$

exposure provided strong evidence of impaired lung function growth with additional evidence of decrements in lung function and the development of asthma. The results of these longitudinal epidemiologic studies were consistent with and extended the evidence that was available in the 2009 PM ISA demonstrating health effects in children due to long-term $PM_{2.5}$ exposure. The conclusion of *"adequate evidence"* for race was based on studies that examined whether there was evidence of increased risk for $PM_{2.5}$-related health effects as well as studies that examined differential exposure by race. Multiple studies reported that minority populations (often defined as non-White populations within individual studies) across different geographical regions are exposed to higher $PM_{2.5}$ concentrations and were at increased risk for $PM_{2.5}$-related mortality, particularly due to long-term exposure. Collectively, the combination of evidence demonstrated that minority populations are at greater risk for both $PM_{2.5}$-related health effects and $PM_{2.5}$ exposure than are Whites.

There was *"suggestive evidence"* that populations with preexisting cardiovascular (2019 PM ISA, Section 12.3.1) or respiratory (2019 PM ISA, Section 12.3.5) disease, those who are overweight or obese (2019 PM ISA, Section 12.3.3), those with particular genetic variants (2019 PM ISA, Section 12.4), those who are of low SES (2019 PM ISA, Section 12.5.3), and those who are current or former smokers (2019 PM ISA, Section 12.6.1) are at increased risk for $PM_{2.5}$-related health effects. Epidemiologic studies that conducted analyses stratified by preexisting cardiovascular disease tended to focus on hypertension, one of the most easily measurable cardiovascular conditions, and did not consistently indicate increased risk for several outcomes examined (e.g., mortality, stroke, BP). However, the strong evidence supporting a *causal relationship* between short- and long-term $PM_{2.5}$ exposure and cardiovascular effects, which included cardiovascular-related mortality and ischemic heart disease (2019 PM ISA, Section 6.1.16 and Section 6.2.18) indicated that individuals with underlying cardiovascular conditions related to these serious outcomes may be at increased risk of a $PM_{2.5}$-related health effect. Similarly, there were few studies that evaluated whether there is evidence of increased risk of a $PM_{2.5}$-related health effect between people with preexisting asthma (2019 PM ISA, Section 12.3.5) and COPD (2019 PM ISA, Section 12.3.5) compared with people that do not have a preexisting respiratory disease. However, epidemiologic studies, particularly those studies examining short-term $PM_{2.5}$ exposure and asthma or COPD ED visits and hospital admissions reported generally consistent positive associations (2019 PM ISA, Section 5.1.2.1 and Section 5.1.4.1), which represent exacerbations that are only possible in people with asthma or COPD. Therefore, there was limited evidence to support that people with preexisting respiratory diseases, specifically asthma or COPD, are at increased risk for a $PM_{2.5}$-related health effect, but there was generally consistent evidence demonstrating these populations experience health effects due to a $PM_{2.5}$ exposure.

Studies that examined whether being obese or overweight increased the risk of a $PM_{2.5}$-related health effect, reported evidence of increased risk for mortality associated with long-term exposures to $PM_{2.5}$, but inconsistent evidence was found for subclinical cardiovascular outcomes, when comparing obese or overweight individuals with normal weight individuals. However, the evaluation of studies

focusing on differences in risk by weight were complicated by the different definitions of obesity used across studies.

The examination of whether specific genetic characteristics dictate increased risk of a $PM_{2.5}$-related health effect involved studies of genetic variants. Across the large number of genetic variants examined there was a consistent trend for increased risk of respiratory and cardiovascular effects associated with $PM_{2.5}$ exposure across gene variants involved in the glutathione transferase pathway. These results were consistent with underlying mechanisms that provided biological plausibility for $PM_{2.5}$-related health effects and have shown that oxidative stress is an early response to $PM_{2.5}$ exposure.

Epidemiologic studies have examined several measures of SES (e.g., income level, educational attainment) in assessing whether populations are at increased risk of a $PM_{2.5}$-related health effect. In studies examining both differential exposure and increased risk of health effects, there was some evidence that low SES populations are more likely to have higher $PM_{2.5}$ exposures and that low SES populations, as measured by metrics for income, are at increased risk of $PM_{2.5}$-related mortality when compared with populations defined as higher SES. Finally, there was some epidemiologic evidence from studies examining long-term $PM_{2.5}$ exposure and lung cancer incidence and mortality, as well as total mortality, that people who currently smoke or were former smokers may be at increased risk of a $PM_{2.5}$-related health effect compared with never smokers.

For the remaining factors evaluated, "*inadequate evidence*" exists to determine whether having diabetes (2019 PM ISA, Section 12.3.2), being in an older lifestage (i.e., older adults; 2019 PM ISA, Section 12.5.1.2), residential location (including proximity to source and urban residence; 2019 PM ISA, Section 12.5.5), sex (2019 PM ISA, Section 12.5.2), or diet (2019 PM ISA, Section 12.6.2) increase the risk of $PM_{2.5}$-related health effects. Across these factors there was either limited assessment of differential risk or exposure (i.e., residential location, diet), or inconsistency in results across studies to support evidence of increased risk of a $PM_{2.5}$-related health effect (i.e., diabetes and sex). Instead, the inconsistency in the evidence makes the determination of disproportionately increased risk more difficult. For example, for older adults (2019 PM ISA, Section 12.5.1.2) there was a relatively small number of studies that examined whether there is evidence of differential risk between age groups. In the evaluation of these studies there was limited evidence indicating that older adults are at increased risk of $PM_{2.5}$-related health effects compared with other age ranges; however, epidemiologic studies focusing only on older adults demonstrated associations with respiratory-related ED visits and hospital admissions with additional, but more limited, evidence of subclinical cardiovascular effects from epidemiologic panel studies and controlled human exposure studies.

2.3. Welfare Effects

Whereas the evaluation of the evidence for PM exposures and health effects was specific to exposure duration (i.e., short- and long-term) and PM size fraction (i.e., $PM_{2.5}$, $PM_{10-2.5}$, and UFP), the

evaluation of the evidence for welfare effects focused generally on whether there was a *causal relationship* between PM and visibility impairment, climate effects, and effects on materials. As detailed below, the evidence continued to support a *causal relationship* between PM and visibility impairment (2019 PM ISA, Section 1.6.1), climate effects (2019 PM ISA, Section 1.6.2), and materials effects (2019 PM ISA, Section 1.6.3).

2.3.1.   Visibility Impairment

It is well known that light extinction from pollution is primarily due to $PM_{2.5}$, resulting in the 2019 PM ISA concluding there is a *causal relationship* between PM and visibility impairment, which was consistent with the conclusions of the 2009 PM ISA (Table 2-3). This conclusion was based on additional characterization of the effect of PM size and composition on light extinction.

The relationship between PM and light extinction has been well documented (2019 PM ISA, Section 13.2.2). Although reconstruction of light extinction is best achieved with detailed information on the size and composition of PM measurements, empirical relationships between light extinction of PM components are more practical and have been successfully evaluated and widely used (2019 PM ISA, Section 13.2.3). Light extinction has been found to vary depending on the available PM species monitoring data, with light extinction efficiencies varying by a factor of 10 between species. Additionally, the variation in PM species by region and season, as well as urban and rural location, can affect light extinction. The steep decline in $PM_{2.5}$ sulfate of −4.6% per year in rural areas and −6.2% per year in urban areas from 2002 to 2012 (2019 PM ISA, Section 1.2.1) has affected the apportionment of light extinction among $PM_{2.5}$ species. Although $PM_{2.5}$ sulfate is still a major contributor to light extinction, visibility in many areas has improved, and a smaller and less seasonally variable fraction of light extinction can be attributed to $PM_{2.5}$ sulfate, with an increasing share due to nitrate and organic matter (2019 PM ISA, Section 13.2.4).

2.3.2.   Climate Effects

Substantial evidence indicates that PM affects the radiative forcing of the climate system, both through direct scattering and absorption of radiation, and indirectly, by altering cloud properties, resulting in the conclusion that there is a *causal relationship* between PM and climate effects, which was consistent with the conclusions of the 2009 PM ISA (2019 PM ISA, Table 1-3). This conclusion was based on multiple studies evaluated in the 2019 PM ISA that have strengthened the evidence for the effects of PM on radiative forcing and have improved the characterization of major sources of uncertainty in estimating PM climate effects, including the indirect radiative forcing effects associated with PM-cloud interactions, and the additional climate effects and feedbacks involving atmospheric circulation and the hydrologic cycle resulting from PM effects on radiative forcing.

Because of these radiative effects, the net effect of PM has been to cool the planet over the last century, masking some of the effects of greenhouse gases on warming (2019 PM ISA, Section 13.3.3). The decrease in PM concentrations in many developed countries over the last few decades has likely contributed to the recent shift toward "global brightening," which may in turn have helped drive rapid warming in North America and Europe because this greenhouse-gas warming was unmasked (2019 PM ISA, Section 13.3.6). In developing countries in Asia, by contrast, PM concentrations have increased over the last several decades, but the associated radiative forcing effects are highly uncertain, due to uncertainties in emissions estimates and the lack of accurate information on the proportion of reflecting versus absorbing species. Although uncertainties in the relationship between PM and climate effects have been further studied and characterized since the 2009 PM ISA, there are still substantial uncertainties with respect to key processes linking PM and climate, specifically the interaction between clouds and aerosols. This is because of the small scale of PM-relevant cloud microphysical processes compared with the coarse resolution of state-of-the-art models, and because of the complex cascade of indirect effects and feedbacks in the climate system that result from a given initial radiative perturbation caused by PM.

2.3.3.   Materials Effects

Multiple studies evaluated in the 2019 PM ISA further characterized soiling and corrosion processes associated with PM and add to the body of evidence of PM damage to materials. Approaches to quantify pollutant exposure corresponding to perceived soiling and damage continue to indicate that deposition can result in increased cleaning and maintenance costs and reduced usefulness of soiled material. The combination of this evidence resulted in the conclusion that there is a *causal relationship* between PM and effects on materials, which was consistent with the conclusions of the 2009 PM ISA (Table 2-3).

Assessments of the relationship between PM and effects on materials have often focused on quantitative assessments including the development of dose-response relationships and application of damage functions to stone used for historic monuments and buildings. Recent studies provided additional information on understanding soiling and corrosion process for glass and metals and have allowed for the development of new dose-response curves (2019 PM ISA, Section 13.4.3), particularly for glass, as well as new damage functions for materials (2019 PM ISA, Section 13.4.4). Additional evidence demonstrated that atmospheric soiling can affect energy costs and climate control, energy consumption of large buildings, and the efficiency of photovoltaic systems (2019 PM ISA, Section 13.4.2).

Table 2-3   Key evidence contributing to *causal* causality determinations for PM exposure and welfare effects evaluated in the 2019 Integrated Science Assessment for Particulate Matter.

Key Evidence in 2019 PM ISA	Welfare Effect Category[a] and Causality Determination

Visibility Impairment and PM Exposure (2019 PM ISA, Section 13.2): Causal Relationship

No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.

Section 13.2.6	Visibility impairment by atmospheric PM, with the strongest effects in the size range from 0.1 to 1.0 μm, was supported by numerous studies summarized in the 1969 PM AQCD (NAPCA, 1969), although the relationship between PM and atmospheric visibility impairment was well established decades earlier. Additional studies supporting the relationship have been described in subsequent documents, and additional new evidence is based on extensive simultaneous network measurements of $PM_{2.5}$ and light extinction.

Climate Effects and PM Exposure (2019 PM ISA, Section 13.3): Causal Relationship

No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.

Section 13.3.9	Effects of PM on radiative forcing of the climate system through both absorption and scattering of radiation directly, as well as through indirect effects involving interactions between PM and cloud droplets, with corresponding effects on temperature, precipitation, and atmospheric circulation, was supported by numerous observational and modeling studies. Research since the 2009 PM ISA (U.S. EPA, 2009) has improved understanding of climate-relevant aerosol properties and processes, as well as characterized key sources of uncertainty in estimating PM climate effects, particularly with respect to PM-cloud interactions.

Materials Effects and PM Exposure (2019 PM ISA, Section 13.4): Causal Relationship

No Change in Causality Determination from the 2009 PM ISA; New Evidence Further Supports the Previous Determination.

Section 13.4.5	Both soiling and corrosion associated with PM contribute to materials damage (U.S. EPA, 2009, 2004, 1982). Deposition of PM can physically affect materials by promoting or accelerating the corrosion of metals, by degrading paints, and by deteriorating building materials such as stone, concrete, and marble. Further characterization of PM effects on glass and metals, along with quantitative dose-response relationships and damage functions for stone and other materials lend additional support to the causal relationship in the 2009 PM ISA. Studies evaluated in the 2019 PM ISA showed that deposition of PM reduces energy efficiency of photovoltaic systems.

AQCD = Air Quality Criteria Document; PM = particulate matter.

[a]The sections referenced in the 2019 PM ISA include a detailed discussion of the available evidence that informed the causality determinations.

3. EVALUATION OF RECENT HEALTH EFFECTS EVIDENCE

The following section focuses on the evaluation of recent health effects studies that fall within the scope of this Supplement as detailed in Section 1.2.2. Within this section the evaluation of recent studies is performed in the context of the studies evaluated and scientific conclusions presented in the Integrated Science Assessment for Particulate Matter (2019 PM ISA). As a result, within each of the following sections, the summary and causality determination from the 2019 PM ISA is presented prior to the evaluation of recent studies published since the literature cutoff date of the 2019 PM ISA that examine the relationship between short-term (i.e., hours up to 1 month) and long-term (i.e., over 1 month to years) $PM_{2.5}$ exposure and cardiovascular effects (Section 3.1) and mortality (Section 3.2).[13] This approach allows for a full accounting of the evidence that formed the basis of the key scientific conclusions in the 2019 PM ISA and the identification of specific sections of the 2019 PM ISA that provide additional details on the total evidence base being considered in the process of reconsidering the 2020 PM NAAQS.

In addition to the evaluation of recent U.S. and Canadian epidemiologic studies that examine the relationship between short-term and long-term $PM_{2.5}$ exposure cardiovascular effects and mortality, this section also evaluates studies that address key scientific topics for which the literature has evolved since the 2020 PM NAAQS review was completed, specifically since the literature cutoff date for the 2019 PM ISA (Section 3.3). These topics that further inform the health effects attributed to $PM_{2.5}$ exposure include experimental studies conducted at near-ambient concentrations (Section 3.3.1), studies that examine the role of $PM_{2.5}$ exposure on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and coronavirus disease 2019 (COVID-19) death (Section 3.3.2), and studies that examine whether there are disparities in exposure to $PM_{2.5}$ or the risk of $PM_{2.5}$-related health effects by race/ethnicity or socioeconomic status (SES).

The studies evaluated in the following sections represent only those studies most informative in considering potential revisions to the PM NAAQS as defined by the scope of this Supplement (Section 1.2.2), that is, U.S. and Canadian epidemiologic studies and other studies that address key scientific topics. Therefore, the scientific information presented in this section does not represent the full multidisciplinary evaluation presented within the 2019 PM ISA, which would lead to the formation of a causality determination. As a result, the summary sections for each health effects category convey how the evidence from recent studies fits within the scientific conclusions of the 2019 PM ISA, and indicates whether recent evidence supports (is consistent with), supports and extends (is consistent with and

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[13]Throughout this Supplement, as detailed in the Preface of the 2019 PM ISA (Section P.3.2.2), risk estimates from epidemiologic studies examining short-term exposures are for a 10 μg/m³ increase in 24-hour avg $PM_{2.5}$ concentrations and long-term exposures are for a 5 μg/m³ increase in annual concentrations, unless otherwise noted.

reduces uncertainties), or does not support (is not consistent with) the causality determinations in the 2019 PM ISA.

3.1. Cardiovascular Effects

3.1.1.   Short-Term PM$_{2.5}$ Exposure

The following sections represent a summary of the evidence and the corresponding causality determination for short-term PM$_{2.5}$ exposure and cardiovascular effects presented in the 2019 PM ISA (Section 3.1.1.1) along with an evaluation of recent epidemiologic studies that fall within the scope of the Supplement (i.e., studies conducted in the U.S. and Canada) and were published since the literature cutoff date of the 2019 PM ISA (Section 3.1.1.2). [14] In addition, with the expansion of epidemiologic studies that used statistical approaches that attempt to more extensively account for confounders and are more robust to model misspecification (i.e., used alternative methods for confounder control), recent studies that employed such methods are also evaluated (Section 3.1.1.3), which can further inform the relationship between short-term PM$_{2.5}$ exposure and cardiovascular morbidity. Finally, a summary of the results of recent studies evaluated in the section is presented in the context of the scientific conclusions detailed in the 2019 PM ISA (Section 3.1.1.4). The evaluation of recent studies presented in this Supplement adds to the collective body of evidence reviewed in the process of reconsidering the PM NAAQS.

3.1.1.1.   Summary and Causality Determination from 2019 Integrated Science Assessment for Particulate Matter

A large body of evidence evaluated in the 2019 PM ISA confirmed and extended the evidence from the 2009 PM ISA (U.S. EPA, 2009) indicating a *causal relationship* between short-term PM$_{2.5}$ exposure and cardiovascular effects. The strongest evidence in the 2009 PM ISA was from epidemiologic studies of emergency department (ED) visits and hospital admissions for ischemic heart disease (IHD) and heart failure, with supporting evidence from epidemiologic studies of cardiovascular mortality. Changes in various measures of cardiovascular function in controlled human exposure studies provided some biological plausibility for these associations. In addition, animal toxicological studies reporting some evidence of reduced myocardial blood flow during ischemia, altered vascular reactivity, and ST segment depression provided additional biological plausibility.

In addition to evaluating evidence across scientific disciplines that examined the relationship between short-term PM$_{2.5}$ exposure and cardiovascular effects, discussed below, the 2019 PM ISA

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[14] Throughout this section, as detailed in the Preface of the 2019 PM ISA (Section P.3.2.2), risk estimates from epidemiologic studies examining short-term exposures are for a 10 μg/m^3 increase in 24-hour avg PM$_{2.5}$ concentrations, unless otherwise noted.

characterized whether evidence supported biologically plausible mechanisms by which short-term $PM_{2.5}$ exposure could lead to cardiovascular effects. This evaluation consisted of an assessment of animal toxicological, controlled human exposure, and epidemiologic studies that examined a range of cardiovascular effects (2019 PM ISA, Section 6.1.1). Plausible mechanisms were identified by which inhalation exposure to $PM_{2.5}$ could progress from initial events to apical events reported in epidemiologic studies (2019 PM ISA, Figure 6-1). The first proposed pathway identified begins as respiratory tract inflammation leading to systemic inflammation. The second proposed pathway identified involves activation of sensory nerve pathways in the respiratory tract that lead to modulation of the autonomic nervous system. Once these pathways are initiated, there is evidence from experimental and observational studies that short-term exposure to $PM_{2.5}$ may result in a series of pathophysiological responses that could lead to cardiovascular events such as ED visits and hospital admissions for IHD and heart failure, and ultimately mortality (2019 PM ISA, Figure 6-1).

In the 2019 PM ISA, evidence supporting the causality determination included generally positive associations from epidemiologic studies of hospital admissions and ED visits for cardiovascular-related effects, and in particular, for IHD and heart failure. Results from these observational studies were supported by experimental evidence from controlled human exposure and animal toxicological studies of endothelial dysfunction, as well as endpoints indicating impaired cardiac function, increased risk of arrhythmia, changes in heart rate variability (HRV), increases in blood pressure (BP), and increases in indicators of systemic inflammation, oxidative stress, and coagulation. Additional results from observational panel studies, although not entirely consistent, provided at least some evidence of increased risk of arrhythmia, decreases in HRV, increases in BP, and ST segment depression. Thus, epidemiologic panel studies also provided some support to the causality determination and to biological plausibility. Finally, epidemiologic studies of cardiovascular-related mortality provided additional evidence that demonstrated a continuum of effects from biomarkers of inflammation and coagulation, subclinical endpoints (e.g., HRV, BP, endothelial dysfunction), ED visits and hospital admissions, and eventually death. The evidence evaluated in the 2019 PM ISA also reduced uncertainties from the previous review related to potential copollutant confounding and limited biological plausibility for cardiovascular effects following short-term $PM_{2.5}$ exposure. Evidence supporting the causality determination for short-term $PM_{2.5}$ exposure and cardiovascular effects reached in the 2019 PM ISA is discussed below and summarized in Table 3-1, using the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015).

Table 3-1   **Summary of evidence for a *causal relationship* between short-term PM₂.₅ exposure and cardiovascular effects from the 2019 Integrated Science Assessment for Particulate Matter.**

Rationale for Causality Determination[a]	Key Evidence[b]	Key References and Sections in the 2019 PM ISA[b]	PM$_{2.5}$ Concentrations Associated with Effects[c] (µg/m³)
Consistent epidemiologic evidence from multiple studies at relevant PM$_{2.5}$ concentrations	Increases in ED visits and hospital admissions for IHD and heart failure in multicity studies conducted in the U.S., Canada, Europe, and Asia Increases in cardiovascular mortality in multicity studies conducted in the U.S., Canada, Europe, and Asia.	Section 6.1.2.1 Section 6.1.3.1 Section 6.1.9	5.8−18.6 5.8−18.0
Evidence from controlled human exposure studies at relevant PM$_{2.5}$ concentrations	Consistent changes in measures of endothelial dysfunction Generally consistent recent evidence for small increases in measures of blood pressure following CAPs exposure Although not entirely consistent, there is additional evidence of conduction abnormalities, heart rate variability, impaired heart function, systemic inflammation/oxidative stress.	Section 6.1.13.2 Section 6.1.6.3 Section 6.1.4.3 Section 6.1.3.2 Section 6.1.10.2 Section 6.1.11.2	24−325 See Tables in identified sections
Consistent evidence from animal toxicological studies at relevant PM$_{2.5}$ concentrations	Consistent changes in indicators of endothelial dysfunction. Additional evidence of changes in impaired heart function, conduction abnormalities/arrhythmia, heart rate variability, blood pressure, systemic inflammation/oxidative stress.	Section 6.1.13.3 Section 6.1.6.4 Section 6.1.4.4 Section 6.1.3.3 Section 6.1.11.3	168.7−510 See Tables in identified sections
Epidemiologic evidence from copollutant models provides some support for an independent PM$_{2.5}$ association	The magnitude of PM$_{2.5}$ associations remain positive, but in some cases are reduced with larger confidence intervals in copollutant models with gaseous pollutants. Further support from copollutant analyses indicates positive associations for cardiovascular mortality. Recent studies that examined potential copollutant confounding are limited to studies conducted in Europe and Asia. When reported, correlations with gaseous copollutants were primarily in the low to moderate range (*r* < 0.7).	Section 6.1.14.1	

Rationale for Causality Determination[a]	Key Evidence[b]	Key References and Sections in the 2019 PM ISA[b]	PM$_{2.5}$ Concentrations Associated with Effects[c] (μg/m³)
Consistent positive epidemiologic evidence for associations between PM$_{2.5}$ exposure and CVD ED visits and hospital admissions across exposure measurement metrics	Positive associations consistently observed across studies that used ground-based (i.e., monitors), model (e.g., CMAQ, dispersion models), and remote sensing (e.g., AOD measurements from satellites) methods, including hybrid methods that combine two or more of these methods.	Kloog et al. (2014)	
Generally consistent evidence for biological plausibility of cardiovascular effects	Strong evidence for coherence of effects across scientific disciplines and biological plausibility for a range of cardiovascular effects in response to short-term PM$_{2.5}$ exposure. Includes evidence for reduced myocardial blood flow, altered vascular reactivity, and ST segment depression.	Section 6.1.1 Figure 6-1	
Uncertainty regarding geographic heterogeneity in PM$_{2.5}$ associations	Multicity U.S. studies demonstrate city-to-city and regional heterogeneity in PM$_{2.5}$-cardiovascular ED visit and hospital admission associations. Evidence supports the supposition that a combination of factors including composition and exposure factors may contribute to the observed heterogeneity.	Section 6.1.2.1 Section 6.1.3.1	

Note: This table corresponds to Table 6-34 in the 2019 PM ISA.

AOD = aerosol optical depth; CMAQ = Community Multiscale Air Quality model; CVD = cardiovascular disease; ED = emergency department; IHD = ischemic heart disease; μg/m³ = micrograms per cubic meter; PM$_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm; ST = beginning of S wave to end of T wave.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described in the 2019 PM ISA.

[c]Describes the PM$_{2.5}$ concentrations with which the evidence is substantiated.

The generally consistent, positive associations observed in numerous epidemiologic studies of ED visits and hospital admissions for IHD, heart failure, and combined cardiovascular-related endpoints contributed to the evidence supporting a *causal relationship* between short-term $PM_{2.5}$ exposure and cardiovascular disease (CVD). Among this body of evidence, nationwide studies of older adults using Medicare reported positive associations between $PM_{2.5}$ concentrations and heart failure hospital admissions (2019 PM ISA, Section 6.1.3.1). Consistent with the results of these large Medicare studies, additional multicity studies conducted in the Northeast U.S. reported positive associations between short-term $PM_{2.5}$ concentrations and ED visits or hospital admissions for IHD (2019 PM ISA, Section 6.1.2.1), whereas studies conducted in the U.S. and Canada reported positive associations between short-term $PM_{2.5}$ concentrations and ED visits for heart failure. Results from epidemiologic studies conducted in single cities contributed additional support to the causality determination but are less consistent and reported both positive and null associations between $PM_{2.5}$ concentrations and these endpoints (2019 PM ISA, Section 6.1.2 and Section 6.1.3). Overall, the body of IHD and heart failure epidemiologic evidence evaluated in the 2019 PM ISA agreed with the evidence from previous ISAs reporting mainly positive associations between short-term $PM_{2.5}$ concentrations and ED visits and hospital admissions. In addition, several controlled human exposure, animal toxicological, and epidemiologic panel studies provided biologically plausible evidence that $PM_{2.5}$ exposure could result in IHD or heart failure through pathways that include endothelial dysfunction, arterial thrombosis, and arrhythmia (2019 PM ISA, Section 6.1.1). Epidemiologic panel studies evaluated in the 2019 PM ISA also supported biological plausibility for IHD and heart failure endpoints by reporting some evidence of ST segment depression (2019 PM ISA, Section 6.1.2.2), with a controlled human exposure study and animal toxicological study showing decreased cardiac function following short-term $PM_{2.5}$ exposure (2019 PM ISA, Section 6.1.3.2 and Section 6.1.3.3).

Results from additional controlled human exposure studies published since the 2009 PM ISA also support a *causal relationship* between short-term $PM_{2.5}$ exposure and cardiovascular effects. The most consistent evidence from these studies is for endothelial dysfunction as measured by changes in brachial artery diameter (BAD) or flow-mediated dilatation (FMD). More specifically, and in contrast to the 2009 PM ISA for which a couple of studies did not find changes in endothelial function, multiple studies evaluated in the 2019 PM ISA that examined the potential for endothelial dysfunction reported an effect of $PM_{2.5}$ on measures of blood flow (2019 PM ISA, Section 6.1.13.2) relative to filtered air (FA) exposure. Nevertheless, all studies were not in agreement with respect to the timing of the effect or the mechanism by which reduced blood flow occurred (i.e., endothelial-independent versus endothelial-dependent mechanisms). In addition to endothelial dysfunction, controlled human exposure studies evaluated in the 2019 PM ISA that used CAPs, but not filtered diesel exhaust (DE), generally reported evidence for small increases in blood pressure, although there were inconsistencies across studies with respect to changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP). It is notable however, that CAPs studies evaluated in the 2019 PM ISA that reported increases in one measure of BP (e.g., SBP), but not the other (e.g., DBP) was found to be statistically significant, that other measure of

BP usually changed as well, but the change was not found to be statistically significant (2019 PM ISA, Section 6.1.6.3). That said, the results of studies evaluated in the 2019 PM ISA are not in agreement with a couple of older controlled human exposure studies that reported no appreciable changes in blood pressure following short-term $PM_{2.5}$ exposure. In addition, although not entirely consistent, there is further evidence from controlled human exposure studies evaluated in the 2019 PM ISA for conduction abnormalities/arrhythmia (2019 PM ISA, Section 6.1.4.3), changes in HRV (2019 PM ISA, Section 6.1.10.2), changes in hemostasis that could promote clot formation (2019 PM ISA, Section 6.1.12.2), and increases in inflammatory cells and markers (2019 PM ISA, Section 6.1.11.2). Thus, although uncertainties remain, controlled human exposure studies are in coherence with epidemiologic studies by demonstrating that short-term exposure to $PM_{2.5}$ may result in the types of cardiovascular endpoints that could lead to ED visits and hospital admissions.

Animal toxicological studies published since the 2009 PM ISA also support a *causal relationship* between short-term $PM_{2.5}$ exposure and cardiovascular effects. A study evaluated in the 2019 PM ISA demonstrated decreased cardiac contractility and left ventricular pressure in mice which was coherent with the results of epidemiologic studies that reported associations between short-term $PM_{2.5}$ exposure and heart failure (2019 PM ISA, Section 6.1.3.3). In addition, like in the controlled human exposure studies, there was generally consistent evidence in animal toxicological studies for indicators of endothelial dysfunction (2019 PM ISA, Section 6.1.13.3). Studies in animals also provided evidence for changes in several other cardiovascular endpoints following short-term $PM_{2.5}$ exposure. Although not entirely consistent, these studies provided at least some evidence of conduction abnormalities and arrhythmia (2019 PM ISA, Section 6.1.4.4), changes in HRV (2019 PM ISA, Section 6.1.10.3), changes in BP (2019 PM ISA, Section 6.1.6.4), and evidence for systemic inflammation and oxidative stress (2019 PM ISA, Section 6.1.11.3). Finally, these toxicological studies also provided evidence indicating that genetic background, diet, and PM composition may influence the effect of short-term $PM_{2.5}$ exposure on some of these health endpoints.

As outlined above, across the scientific disciplines, there is evidence for a continuum of cardiovascular-related health effects following short-term exposure to $PM_{2.5}$. These effects ranged from relatively modest increases in biomarkers related to inflammation and coagulation, to subclinical CVD endpoints such as endothelial dysfunction, to ED visits and hospital admissions for outcomes such as IHD and heart failure. This continuum of effects is supported by epidemiologic studies that reported a relatively consistent relationship between short-term $PM_{2.5}$ exposure and CVD-related mortality. These epidemiologic studies also reduced a key uncertainty from the 2009 PM ISA by providing evidence that gaseous pollutants are not likely to confound the $PM_{2.5}$-cardiovascular mortality relationship.

Taken together, the evidence described within the 2019 PM ISA extends the consistency and coherence of the evidence base reported in the 2009 PM ISA and 2004 AQCD. Direct evidence for $PM_{2.5}$ exposure-related cardiovascular effects can be found in several controlled human exposure and animal toxicological studies. In coherence with these results are epidemiologic panel studies also finding that

$PM_{2.5}$ exposure is associated with some of the same cardiovascular endpoints reported in controlled human exposure and animal toxicological studies. The number of studies is limited that evaluate these endpoints, and there are some inconsistencies in results across some animal toxicological, controlled human exposure, and epidemiologic panel studies—although this may be due to substantial differences in study design, study populations, or differences in PM composition across air sheds. Nonetheless, the results from these epidemiologic panel, controlled human exposure, and animal toxicological studies, in particular those related to endothelial dysfunction, impaired cardiac function, ST segment depression, thrombosis, conduction abnormalities, and BP, provide coherence and biological plausibility for the consistent results from epidemiologic studies that reported positive associations between short-term $PM_{2.5}$ concentrations and IHD and heart failure, and ultimately cardiovascular mortality. **Overall, considering the entire evidence base, the evidence continues to be sufficient to conclude that a causal relationship exists between short-term $PM_{2.5}$ exposure and cardiovascular effects.**

3.1.1.2.   Recent U.S. and Canadian Epidemiologic Studies

Recent epidemiologic studies conducted in the U.S. and Canada build on the strong epidemiologic evidence base evaluated in the 2019 PM ISA, as well as in previous assessments, which provided the scientific rationale supporting a *causal relationship* between short-term $PM_{2.5}$ exposure and cardiovascular effects (Section 3.1.1.1). In addition to examining the relationship between short-term $PM_{2.5}$ exposure and specific cardiovascular outcomes (i.e., IHD and myocardial infarction [Section 3.1.1.2.1], cerebrovascular disease and stroke [Section 3.1.1.2.2], heart failure [Section 3.1.1.2.3], arrhythmia [Section 3.1.1.2.4], combined cardiovascular effects [Section 3.1.1.2.5], and cardiovascular mortality [Section 3.1.1.2.6]), analyses within these recent studies also further examined issues relevant to expanding the overall understanding of the effect of short-term $PM_{2.5}$ exposure on cardiovascular outcomes. Specifically, recent studies assessed potential copollutant confounding (Section 3.1.1.2.7) and the lag structure of associations (Section 3.1.1.2.8). The following sections present an evaluation of recent epidemiologic studies conducted in the U.S. and Canada that inform each of the aforementioned topics within the context of the evidence base evaluated and summarized in the 2019 PM ISA. Study-specific details (e.g., study population, exposure assessment approach, confounders considered) for the epidemiologic studies evaluated in this section are presented in Appendix A (Table A-1).

3.1.1.2.1.   Ischemic Heart Disease and Myocardial Infarction

IHD is a chronic condition characterized by atherosclerosis and reduced blood flow to the heart. Myocardial infarction (MI), more commonly known as a heart attack, occurs when heart tissue death occurs that is secondary to prolonged ischemia. The effect of short-term $PM_{2.5}$ exposure on acute MI, complications from recent MI, and other acute or chronic IHD are generally evaluated using International

Classification of Diseases (ICD) codes recorded when a patient is admitted or discharged from the hospital or ED (ICD-Ninth Revision [ICD-9]: 410−414 or ICD-Tenth Revision [ICD-10]: I20−I25). In experimental or epidemiologic panel studies, indicators of MI include ST segment depression as measured by an electrocardiograph (ECG). The ST segment of an electrocardiogram recorded by surface electrodes corresponds to the electrical activity of the heart registered between ventricular depolarization and repolarization and is normally isoelectric.

The epidemiologic studies reviewed in the 2019 PM ISA (U.S. EPA, 2019) strengthened the evidence characterized in the previous ISA (U.S. EPA, 2009). Most of the evidence for IHD and MI in the 2009 PM ISA was from multicity epidemiologic studies of ED visits and hospital admissions [i.e., the U.S. Medicare Cohort Air Pollution Study (MCAPS) (Dominici et al., 2006), a four-city study in Australia (Barnett et al., 2006), and a study among older adults in several French cities (Host et al., 2008)]. The positive associations reported in these studies were an important line of evidence in the 2009 PM ISA concluding a *causal relationship* between short-term $PM_{2.5}$ exposure and cardiovascular effects. Uncertainties noted in the 2009 PM ISA with respect to exposure measurement error for those not living near a $PM_{2.5}$ monitor were reduced in the 2019 PM ISA with the consideration of studies that applied hybrid exposure assessment techniques that combine land use regression data with satellite aerosol optical depth (AOD) measurements and $PM_{2.5}$ concentrations measured at fixed-site monitors to estimate $PM_{2.5}$ concentrations. Further, compared with the 2009 PM ISA, the evidence in the 2019 PM ISA was expanded to include studies examining the association of short-term $PM_{2.5}$ exposure ST segment depression in addition to ED visits and hospital admissions for MI.

A recent study extends the evidence presented in the 2019 PM ISA through its examination of the association between short-term $PM_{2.5}$ exposure with hospital admissions for MI among the low-income and/or disabled Americans comprising the Medicaid population (deSouza et al., 2021). deSouza et al. (2021) reported a positive association between $PM_{2.5}$ concentration (0−1 day average) and acute MI (OR: 1.1 [95% CI: 1.03, 1.7]). Recent studies have also addressed methodological challenges. Specifically, Krall et al. (2018) conducted an analysis to elucidate the interpretation of potentially uncertain single-city estimates. These authors used Poisson time-series regression to estimate the associations of 24-hour average $PM_{2.5}$ concentration (lag Day 0) with ED visits for IHD and other cardiovascular outcomes for each of the five cities included in their study. To estimate the association across all cities and the posterior city-specific associations, they fit both traditional Bayesian hierarchical models in which associations were estimated for each outcome separately, and multi-cause multicity (MCM) Bayesian hierarchical models in which multiple cardiovascular outcomes were included in the model simultaneously so that a shared between-city variation could be estimated. The authors also performed analyses to determine whether their results were sensitive to the choice of exposure lag (Section 3.1.1.2.8) or the specification of time trends. The associations between 24-hour $PM_{2.5}$ concentration and IHD ED visits in the traditional multicity model was 1.009 (95% Posterior Interval [PI]: 0.993, 1.025). The comparable association (1.009 [95% PI: 0.998, 1.022]) using MCM was more precise (i.e., narrower confidence intervals). As expected, the city specific estimates were relatively uncertain and heterogeneous across cities when there were a

small number of daily ED visits. In another recent study, Leiser et al. (2019) designed an analysis to examine the association between short-term $PM_{2.5}$ exposure and IHD and MI hospital admissions in which the competing risk of mortality was controlled and differences across sex and age categories were examined. These authors used Medicare data for residents, 65 years and older, of the contiguous counties of the Wasatch Front in Utah to examine the association between $PM_{2.5}$ concentration and cardiac hospital re-admissions within 30 days of an index hospitalization, controlling for competing mortality risk. These authors found an association of 3-day average $PM_{2.5}$ concentration (lag 0−2 day) with IHD (HR: 1.03 [95% CI: 0.96, 1.12]) and MI (HR: 1.03 [95% CI: 0.92, 1.16]). Confidence intervals for the age- and sex-stratified results, which were conducted to evaluate potential modification of the association, were generally overlapping.

In another analysis of older adults using Medicare data, Wei et al. (2019) estimated the association of short-term $PM_{2.5}$ exposure with MI hospital admissions and a range of other health conditions, including some diseases that are rarely studied in relationship to $PM_{2.5}$ exposure. Hospital admission data were ascertained using discharge data recorded for Medicare inpatient hospital claims in the continental U.S. (2000−2012). Rather than report a relative risk (RR) estimate, the authors reported the absolute risk per 10 million person-days associated with each 1 unit increase in lag 0−1 $PM_{2.5}$ concentration (i.e., 0.29 [95% CI: 0.17, 0.40]).

Recent single city studies also add to the evidence base presented in the 2019 PM ISA. Liu et al. (2020) examined the modification of the association between short-term $PM_{2.5}$ exposure and MI hospital admissions by long-term NO_2 exposure. These authors performed a case-crossover study to estimate the association of short-term exposure to $PM_{2.5}$ among individuals living in Calgary neighborhoods with higher long-term NO2 exposure (2004−2012). No association between 0−2-day average $PM_{2.5}$ concentration with hospital admissions for MI among the entire population was observed [OR: 1.03 (95% CI: 0.96, 1.12)]. The association was null in the lowest tertile of long-term NO_2 concentration (OR: 0.94 [95% CI: 0.86, 1.18]), but the association strengthened in terms of magnitude and precision with increasing NO_2 concentration tertile (tertile 2, OR: 1.04 [95% CI: 0.94, 1.18]) and (tertile 3, OR: 1.10 [95% CI: 1.00, 1.19]). In addition, an extended analysis of a study reviewed in the 2019 PM ISA supports previous results that found a positive association between short-term $PM_{2.5}$ exposure and ST elevation myocardial infarction (STEMI) (Evans et al., 2017). Specifically, Evans et al. (2017) performed a case-crossover analysis to examine the relationship between short-term $PM_{2.5}$ concentration and STEMI in acute coronary syndrome or unstable angina patients (n = 362) in Monroe County, NY (2007−2012). The association between previous 1-hour $PM_{2.5}$ concentration and STEMI reported by these authors (OR: 1.25 [95% CI: 0.99, 1.59]) was virtually identical to the association (OR: 1.26 [95% CI: 1.01, 1.57]) reported in a previous analysis of this population conducted by Gardner et al. (2014) that reported fewer patients (n = 338) and a shorter follow-up time (2007−2010).

Results of studies of IHD and MI included in the 2009 PM ISA, the 2019 PM ISA and recent studies published since the literature cutoff date of the 2019 PM ISA are summarized in Figure 3-1.

Overall, recent studies support and extend the findings of the 2019 PM ISA with additional studies reporting positive associations between short-term $PM_{2.5}$ exposure and both IHD and MI hospital admissions and ED visits.

Study	Outcome	Location	Mean (µg/m3)	Lag	Notes
Dominici et al. (2006)	IHD	204 U.S. Counties	13.4	2	Ages 65+
Barnett et al. (2006)	IHD	4 Australian Cities	8.1-9.7	0-1	Ages 65+
Host et al. (2007)	IHD	6 French Cities	13.8-18.6	0-1	Ages 65+
†Bell et al. (2015)	IHD	213 U.S. Counties	12.3	0	Ages 65+
†Kloog et al. (2014)	IHD	7 Mid-Atlantic States	11.9	0-1	Ages 65+
Zanobetti et al. (2006)	MI	Boston, MA	11.1	0	Ages 65+
†Bell et al. (2015)	MI	213 U.S. Counties	12.3	0	Ages 65+
†Zanobetti et al. (2009)	MI	26 U.S. Cities	15.3	0-1	Ages 65+
*DeSouza et al. (2019)	MI	U.S. (National)	11.5	0-1	Medicaid
†Haley et al. (2009)		8 New York Cities	5.8	0	
*Krall et al. (2018)	IHD	5 Cities, U.S.	10.8-15.4	0	Traditional Multicity
				0	MCM Multicity
†Hsu et al. (2017)	IHD	4 NY Regions	NR	0	NYC, Long Island & Hudson
				0	Adirondack & North
				0	Mohawk Valley & Binghamton
				0	Central & Western NY
†Talbott et al. (2014)	IHD	7 U.S. States	6.5-12.8	0-2	Florida
				0-2	Massachusetts
				0-2	New Jersey
				0-2	New Hampshire
				0-2	New Mexico
				0-2	New York
				0-2	Washington
†Ostro et al. (2016)	IHD	8 CA counties	16.5	0	
†Milojevic et al. (2014)	IHD	15 Conurbations, UK	10	0-4	
†Samat et al. (2015)	IHD	St. Louis, MO	18	0-2	
†Milojevic et al. (2014)	MI	15 Conurbations, UK	10	0-4	
				0-4	STEMI
				0-4	NSTEMI
†Stieb et al. (2009)	Angina/MI	6 Canadian Cities	6.7-9.8	0	
†Szyskowicz et al. (2009)	Angina	6 Canadian Cities	8.3	0	
†Weichenthal et al. (2016)	MI	16 Cities Ontario	6.9	0-2	
*Liu et al. (2020)	MI	Alberta, Canada	9.79	0-2	Overall
					High NO2
†Talbott et al. (2014)	MI	7 U.S. States	6.5-12.8	0-2	Florida
				0-2	Massachusetts
				0-2	New Jersey
				0-2	New Hampshire
				0-2	New Mexico
				0-2	New York
				0-2	Washington
†Ostro et al. (2016)	MI	8 CA counties	16.5	0	
†Rich et al. (2010)	MI	New Jersey state	7.6-12.3	0-23h	
				0-23h	Transmural MI
				0-23h	Non-Transmural MI
†Pope et al. (2015)	MI	Utah, USA	9.9-10.6	0	STEMI
				0	NSTEMI
				0	Unstable Angina
*Leiser et al. (2019)	IHD	4 counties, Utah, U.S.	10.96	0-2	30 d Readmission
	MI				30 d Readmission
*Evans et al. (2017)	MI	Rochester, NY	17.1	1 h	STEMI
†Gardner et al. (2014)	MI	Rochester, NY	8	0-1	STEMI
	MI			0-1	NSTEMI

Relative Risk (95% CI)

Source: Update of Figure 6-2, 2019 PM ISA.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. IHD = ischemic heart disease, MCM = multi-cause multicity; MI = myocardial infarction, NR = not reported; NSTEMI = non-ST segment elevation MI, STEMI = ST- elevation MI. Risk estimates are standardized to a 10 µg/m^3 increase in PM$_{2.5}$ concentrations.

Figure 3-1   Results of studies of short-term PM$_{2.5}$ exposure and hospital admissions and emergency department visits for ischemic heart disease.

3.1.1.2.2.   Cerebrovascular Disease and Stroke

Cerebrovascular disease (CBVD) typically includes conditions classified under ICD-10 codes I60−I69 (ICD-9: 430−438) such as hemorrhagic stroke (HS), cerebral infarction (i.e., ischemic stroke [IS]) and occlusion of the precerebral and cerebral arteries. IS results from an obstruction within a blood vessel that supplies oxygen to the brain, potentially leading to infarction, and accounts for 87% of all strokes (Goldberger et al., 2008). Hemorrhagic stroke is less common but results in a disproportionate number of fatalities. The HS subtype results from a brain aneurysm or leaking vessel in the brain and can be further categorized by brain region (e.g., intracerebral, or subarachnoid). Comorbidities that increase stroke risk but may also be associated with $PM_{2.5}$ exposure include hypertension, diabetes, CHD, and atrial fibrillation. The 2009 PM ISA and the 2019 PM ISA described inconsistent results across epidemiologic studies that considered the relationship between short-term $PM_{2.5}$ exposure and ED visits and hospital admissions for CBVD, with most studies reporting a lack of an association. Evidence relating to various stroke subtypes was also inconsistent. Results from recent studies of the association between short-term $PM_{2.5}$ concentration and stroke expand the evidence but remain inconsistent overall. Specifically, a study of Medicaid recipients found a large magnitude positive association, while several analyses of established cohorts (Health Professionals Follow-Up [HPFU] study, Women's Health Initiative [WHI], REasons for Geographic and Racial Differences in Stroke [REGARDS]) report null or inverse associations with stroke regardless of subtype.

Recent studies that analyze data from participants enrolled in several established cohort studies expand the evidence pertaining to stroke subtype. Fisher et al. (2019) estimated the associations of short-term $PM_{2.5}$ exposure with several stroke types, which were ascertained through self-report and expert medical record review, among men enrolled in the HPFU study. The authors reported no evidence of positive associations between lag 0 to 3-day average $PM_{2.5}$ concentration and total stroke (OR: 0.93 [95% CI: 0.78, 1.11]), ischemic (OR: 0.99 [95% CI: 0.81, 1.20]), hemorrhagic (OR: 0.80 [95% CI: 0.50, 1.27]), undetermined type (OR: 0.56 [95% CI: 0.26, 1.24]), and nonfatal stroke (OR: 1.05 [95% CI: 0.84, 1.27]). The authors also evaluated whether factors including age, BMI, smoking status, diabetes mellitus, hypertension, hypercholesterolemia, and current aspirin use potentially modified the associations with IS or HS; however, the number of stroke events within each strata was small and no statistical evidence of heterogeneity between stratified estimates was reported based on chi-square tests of model homogeneity. Sun et al. (2019) also estimated the association of short-term $PM_{2.5}$ with total, hemorrhagic, and ischemic stroke but studied a different population (i.e., post-menopausal women enrolled in the WHI study). Stroke was ascertained through self-report and physician adjudication. Three-day average $PM_{2.5}$ concentration (lag 0−2) was not associated with total (OR: 0.98 [95% CI: 0.92, 1.02]), ischemic (OR: 0.96 [95% CI: 0.90, 1.02]), or hemorrhagic stroke (OR: 1.02 [95% CI: 0.90, 1.17]) in this study. The authors also conducted stratified analysis to examine whether associations varied across categories of age at stroke onset, U.S. census region, smoking status, body mass index, and prior history of diabetes mellitus, hypertension, heart or circulation problems, or arterial fibrillation at enrollment. Across these different

stratified analyses, only when examining the stratum for obese women was there some evidence that the association of total stroke with $PM_{2.5}$ may be increased. Finally, McClure et al. (2017) performed a case-cross over analysis among participants in the REGARDS study to determine the association between $PM_{2.5}$ exposure at single-day lags (1, 2, and 3 day lags) and stroke ascertained through self-report followed by a medical record. The REGARDS study oversampled participants in several southern states where stroke risk is high among Black residents in order to study geographic and racial differences in stroke. $PM_{2.5}$ concentration was dichotomized (≤ 12 μg/m^3 versus 12 to 150.4 μg/m^3) and the odds of stroke in the higher category was compared with the odds of stroke in the lower category. After adjustment for temperature and relative humidity, no association was reported between $PM_{2.5}$ exposure and stroke, regardless of the lag examined (OR: 0.99 [95% CI: 0.83, 1.19], lag 1). This finding persisted regardless of stroke subtype or exposure lag. Overall, analyses from three established and diverse cohorts did not present evidence of an association between short-term $PM_{2.5}$ exposure and stroke.

Unlike the analyses described above, deSouza et al. (2021) examined the relationship between $PM_{2.5}$ concentration (0−1 day average) and hospital admissions for IS among the low-income and/or disabled Americans comprising the Medicaid population. The OR for the association between $PM_{2.5}$ (lag 0−1 day average) and IS was 1.12 (95% CI: 1.04, 1.20). In a study designed to gain an understanding of the heterogeneity in results across single-city studies, Krall et al. (2018) examined the associations of 24-hour $PM_{2.5}$ concentration (lag 0) with ED visits for stroke. These authors estimated the associations across five cities using a traditional Bayesian hierarchical approach and a MCM Bayesian hierarchical model in which all outcomes were modeled simultaneously. The association of 24-hour $PM_{2.5}$ concentration (lag 0) with ED visits for stroke was 1.008 (95% CI: 0.984, 1.034) in the traditional multicity model and more precise (i.e., narrower confidence intervals) 1.008 (95% PI: 0.995, 1.021) in the MCM model. However, in a single city study of recurrent IS in Nueces county Texas, Wing et al. (2017) did not report evidence of an association between $PM_{2.5}$ concentration during the previous day (lag 1), and the odds of recurrent stroke (OR: 0.95 (95% CI: 0.71−1.28]).

Results of studies of short-term exposure to $PM_{2.5}$ and ED visits or hospital admissions for stroke included in the 2009 PM ISA, the 2019 PM ISA and recent studies published since the literature cutoff date of the 2019 PM ISA are summarized in Figure 3-2. The epidemiologic evidence for an association between short-term $PM_{2.5}$ and various stroke subtypes assessed in the 2019 PM ISA was characterized as inconsistent and limited. Some recent studies report evidence of a positive association with stroke while others report null or inverse associations. Therefore, the evidence pertaining to the effect of short-term $PM_{2.5}$ exposure and stroke remains inconsistent overall.
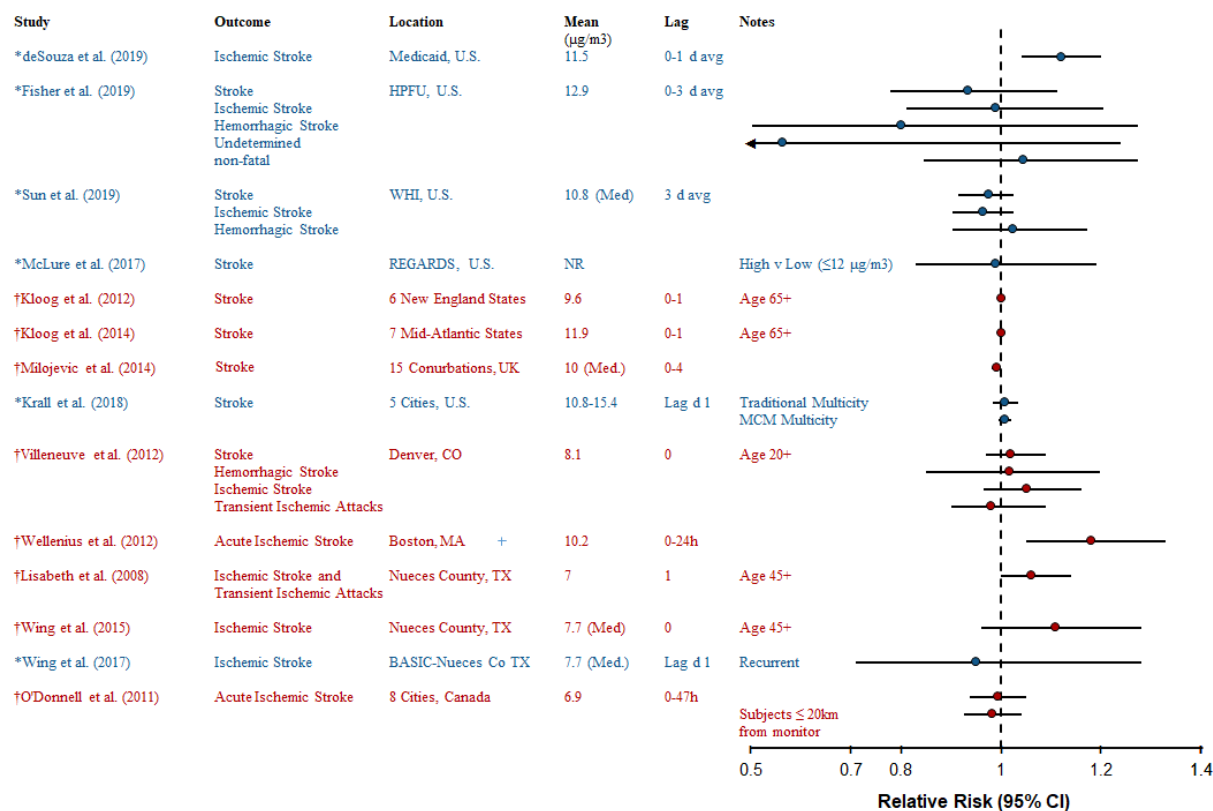
Source: Update of Figure 6-5, 2019 PM ISA.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. NR = not reported. Risk estimates are standardized to a 10 µg/m^3 increase in PM$_{2.5}$ concentrations.

Figure 3-2   Results of studies of short-term PM$_{2.5}$ exposure and hospital admissions and emergency department visits for stroke.

3.1.1.2.3.   Heart Failure

Heart failure (HF) refers to a set of conditions in which pumping action of the heart is weakened. In congestive heart failure (CHF), the flow of blood from the heart slows, failing to meet the oxygen demands of the body, and returning blood can back up, causing swelling or edema in the lungs or other tissues (typically in the legs and ankles). The effect of short-term $PM_{2.5}$ exposure on people with CHF—which is a chronic condition—is generally evaluated using ICD codes recorded when a patient is admitted or discharged from the hospital or ED. The relevant diagnostic codes for heart failure are ICD-9 428 and ICD-10 I50. These codes encompass left, systolic, diastolic, and combined heart failure. Similar to the other cardiovascular outcomes, the majority of the evidence in the 2009 PM ISA was from epidemiologic studies of hospital admissions and ED visits [i.e., multicity studies in the U.S.(Dominici et al., 2006) and Australia (Barnett et al., 2006)]. Studies evaluated in the 2019 PM ISA strengthened this line of evidence with additional multicity epidemiologic studies conducted in the U.S., Canada, and Europe generally reporting positive associations between short-term $PM_{2.5}$ exposure and hospital admissions and ED visits for HF. Results from single-city studies tended to be less consistent. Several recent studies add to the body of evidence providing additional support for a positive association between short-term $PM_{2.5}$ exposure and ED visits and hospital admissions for exacerbations of HF.

Recent studies conducted examined the association of short-term $PM_{2.5}$ exposure with readmission to the hospital for HF within 30 days of an index hospitalization. Leiser et al. (2019) used Medicare data to examine the association of short-term $PM_{2.5}$ exposure and cardiac hospital re-admissions among older adults within 30 days of the index hospitalization. These authors reported an association of 3-day average $PM_{2.5}$ concentration (lag 0−2 day) with readmission for HF (HR: 1.10 [95% CI: 1.03, 1.19]). Confidence intervals of the age and sex stratified results were generally overlapping. In another study of 30-day hospital readmission, Wyatt et al. (2020c) characterized the association of short-term $PM_{2.5}$ exposure with CHF among end-stage renal disease patients (i.e., those undergoing hemodialysis). Both readmission within 1 to 7 days and readmission between 8 to 30 days was evaluated. The RR for the association of 24-hour $PM_{2.5}$ concentration (lag 0) with HF readmission within 1−7 days was 1.37 (95% CI: 1.14, 1.60). The association with late readmission (8−30 days) was 1.41 (95% CI: 1.25, 1.58). In another unique population, deSouza et al. (2021) estimated the association of $PM_{2.5}$ concentration (0−1 day average) with CHF hospital admissions among the low-income and/or disabled Americans comprising the Medicaid population. The OR for the association between $PM_{2.5}$ (lag 0−1 day average) and CHF was 1.10 (95% CI: 1.04, 1.16).

In addition to the studies described above that focus on 30-day hospital readmission, Krall et al. (2018) examined the association of 24-hour $PM_{2.5}$ concentration (lag Day 0) with ED visits for CHF in an analysis in five cites that was designed to compare methods used for multicity studies. These authors estimated the multicity associations using a traditional Bayesian hierarchical approach and a MCM Bayesian hierarchical model in which all outcomes were modeled simultaneously. The association of 24-hour $PM_{2.5}$ concentration (lag 0) with CHF was 1.003 (95% CI: 0.986, 1.021) in the traditional

multicity model and 1.003 (95% PI: 0.992, 1.016) in the MCM model. In another study, Wei et al. (2019) used Medicare data (i.e., inpatient hospital claims) to estimate the association of short-term $PM_{2.5}$ exposure with CHF hospital admissions in the continental U.S. between 2000 and 2012. Rather than report a RR estimate, the authors reported the absolute increase in risk of admission to hospital per 10 million person-days associated with each 1 $\mu g/m^3$ increase in lag 0−1 $PM_{2.5}$ (i.e., 0.68 [95% CI: 0.52 to 0.84]).

Results of studies of HF included in the 2009 PM ISA, the 2019 PM ISA and recent studies published since the literature cutoff date of the 2019 PM ISA are summarized in Figure 3-3. Overall, these studies support and extend the limited evidence in the 2019 PM ISA, reporting positive associations between short-term $PM_{2.5}$ exposure and HF.

Study	Outcome		Mean (μg/m3)	Lag	Notes
Dominici et al. (2006)	HF	204 U.S. Counties	13.4	0	Ages 65+
Barnett et al. (2006)	HF	4 Australian Cities	8.1-9.7	0-1	Ages 14-64
				0-1	Ages 65+
†Bell et al. (2015)	HF	213 U.S. Counties	12.3	0	Ages 65+
†Zanobetti et al. (2009)	HF	26 U.S. Cities	15.3	0-1	Ages 65+
*DeSouza et al. (2019)	HF	Medicaid, U.S.	11.5	0-1	
†Talbott et al. (2014)	HF	7 U.S. States	6.5-12.8	0-2	Florida
				0-2	Massachusetts
				0-2	New Jersey
				0-2	New Hampshire
				0-2	New Mexico
				0-2	New York
				0-2	Washington
†Hsu et al. (2017)	HF	4 NY Regions	NR	0	NYC, Long Island & Hudson
				0	Adirondack & North
				0	Mohawk Valley & Binghamton
				0	Central & Western NY
†Haley et al. (2009)	HF	8 New York Cities	5.8	0	
*Krall et al. (2018)	HF	5 Cities, U.S.	10.8-15.4	0	Traditional Multicity
					MCM Multicity
†Ostro et al. (2016)	HF	8 CA counties	16.5	0	
†Stieb et al. (2009)	HF	6 Canadian Cities	8.2	0	
†Milojevic et al. (2014)	HF	15 Conurbations, UK	10 (Med.)	0-4	
†Rodopoulou et al. (2015)	HF, HHD	Little Rock, AR	12.4	1	
†Sarnat et al. (2015)	HF	St. Louis, MO	18	0-2	
*Leiser et al. (2019)	HF	Wasatch Front, Utah	11	0-2	30 day readmit
*Wyatt et al. (2020)	HF	ESRD Patient	9.3	0	0-7 d readmission
					8-30 d readmission

Relative Risk (95% CI)

Source: Update of Figure 6-3, 2019 PM ISA.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. ESRD = end-stage renal disease; HF = heart failure, HHD = hypertensive heart disease, NR = not reported; re-HA = readmission to the hospital for heart failure. Risk estimates are standardized to a 10 μg/m^3 increase in PM$_{2.5}$ concentrations.

Figure 3-3   Results of studies of short-term PM$_{2.5}$ exposure and hospital admissions and emergency department visits for heart failure.
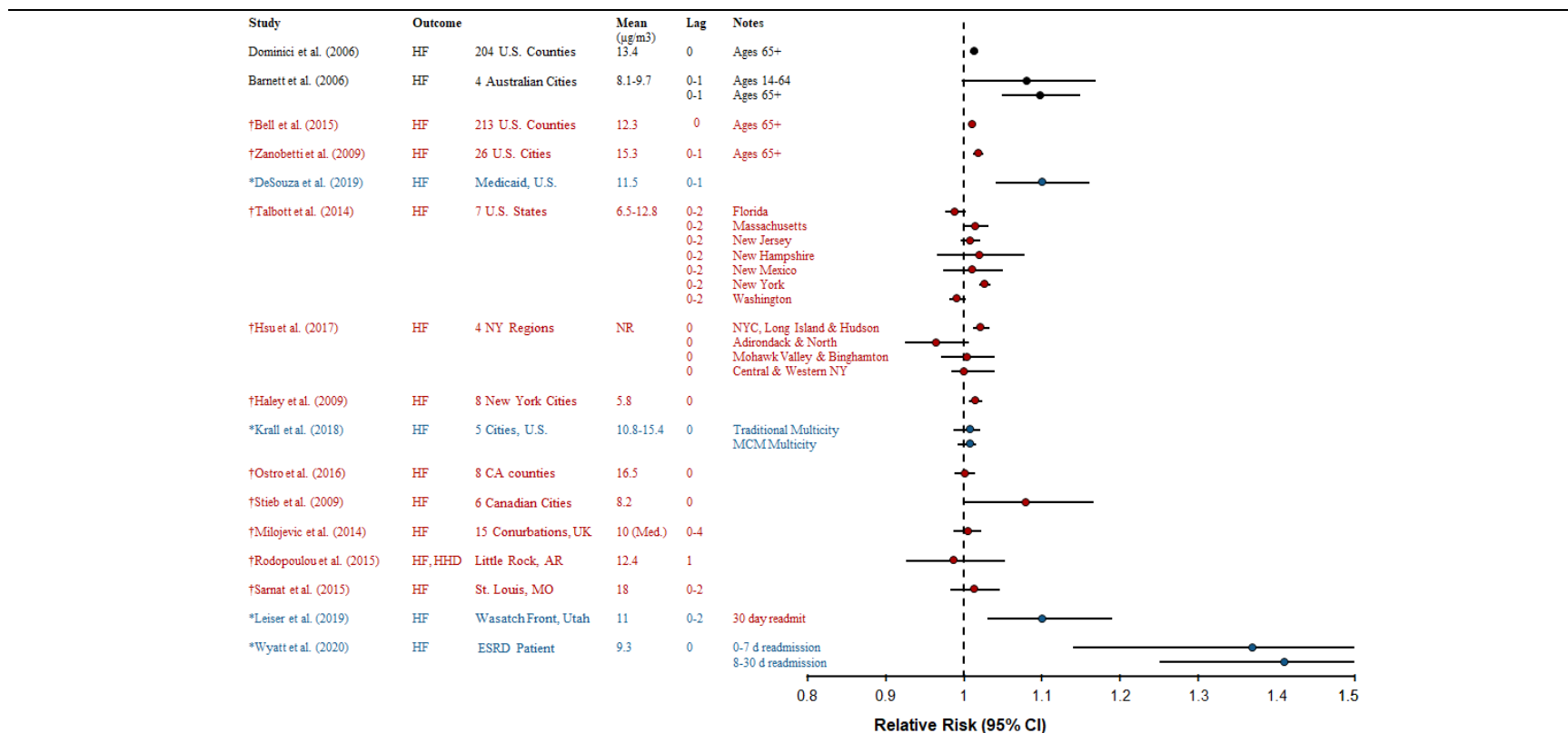
May 2022   3-18

3.1.1.2.4.   Arrhythmia

In epidemiologic studies, the association between short-term $PM_{2.5}$ exposure and arrhythmia is generally evaluated using ICD codes (ICD-9 427 or ICD-10 149.9) for hospital admissions and ED visits. Out-of-hospital cardiac arrests (OHCA) that typically result from ventricular arrhythmia were evaluated with the body of evidence pertaining to arrhythmia. Overall, the evidence evaluated in the 2009 PM ISA and the 2019 PM ISA was limited. However, in the 2019 PM ISA, some evidence from epidemiologic panel studies indicated an association between short-term $PM_{2.5}$ exposure and potential indicators of arrhythmia (e.g., ectopic beats and tachycardia). The small number of recent studies support a positive association of short-term $PM_{2.5}$ exposure with arrythmias.

Recent studies examined the association of short-term exposure to $PM_{2.5}$ and dysrhythmia adding to the limited evidence evaluated in the 2019 PM ISA. Wyatt et al. (2020c) examined 30-day hospital re-admission among end-stage renal disease patients (i.e., those undergoing hemodialysis). Both early re-admission within 1 to 7 days and later readmission after 8 to 30 days was evaluated. The RR for the association of 24-hour $PM_{2.5}$ concentration (lag 0) with dysrhythmia and conduction disorder readmissions within 1−7 days was 1.48 (95% CI: 1.23, 1.74). The association with late re-admission (8−30 days) was 1.31 (95% CI: 1.13, 1.50). In another study of 30-day hospital re-admission, Leiser et al. (2019) estimated the association of $PM_{2.5}$ concentration and cardiac arrhythmia among Medicare beneficiaries who survived a cardiovascular event, and examined differences across sex and age in models that adjusted for the competing risk of readmission due to a non-cardiovascular cause or death. These authors reported an inverse association of 3-day average $PM_{2.5}$ concentration (lag 0−2 days) with re-admission for dysrhythmia or arrhythmia (HR: 0.88 [95% CI: 0.75, 1.02]). Confidence intervals of the age and sex stratified results were generally overlapping and did not provide evidence of effect modification. Krall et al. (2018) examined the association of 24-hour $PM_{2.5}$ concentration (lag Day 0) with CVD ED visits in an analysis designed to compare methods for multicity analyses. These authors estimated the associations with CVD ED visits including visit for dysrhythmia across five cities using a traditional Bayesian hierarchical approach and a MCM Bayesian hierarchical model in which all outcomes were modeled simultaneously. The association between 24-hour $PM_{2.5}$ concentration (lag 0) with ED visits for dysrhythmia was 1.009 (95% CI: 0.993, 1.023) in the traditional Bayesian hierarchical model and 1.009 (95% PI: 0.998, 1.022) in the MCM Bayesian hierarchical model. Finally, Wei et al. (2019) estimated the association of short-term $PM_{2.5}$ exposure with arrhythmia hospital admissions in a study using discharge data recorded for Medicare inpatient hospital claims in the continental the U.S. (2000−2012). Rather than report a RR estimate, the authors reported the absolute increase in risk of admission to hospital per 10 million person-days associated with each 1 μg/m^3 increase in lag 0−1 $PM_{2.5}$ concentration (i.e., 0.26 [95% CI: 0.13 to 0.38]).

Results of studies of arrythmia included in the 2009 PM ISA, the 2019 PM ISA and recent studies published since the 2019 PM ISA are summarized in Figure 3-4. Overall, these studies extend the limited evidence evaluated in the 2019 PM ISA as they report positive associations between short-term $PM_{2.5}$

exposure and arrhythmia in most studies. However, an analysis of Medicare recipients in Utah that adjusted for the competing risk of readmission for a non-cardiovascular cause or death reported an inverse association.

Source: Update of Figure 6-4, 2019 PM ISA.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. HF = heart failure, HHD = hypertensive heart disease, NR = not reported. Risk estimates are standardized to a 10 µg/m^3 increase in PM$_{2.5}$ concentrations.

Figure 3-4   **Results of studies of short-term PM$_{2.5}$ exposure and hospital admissions and emergency department visits for arrhythmia.**
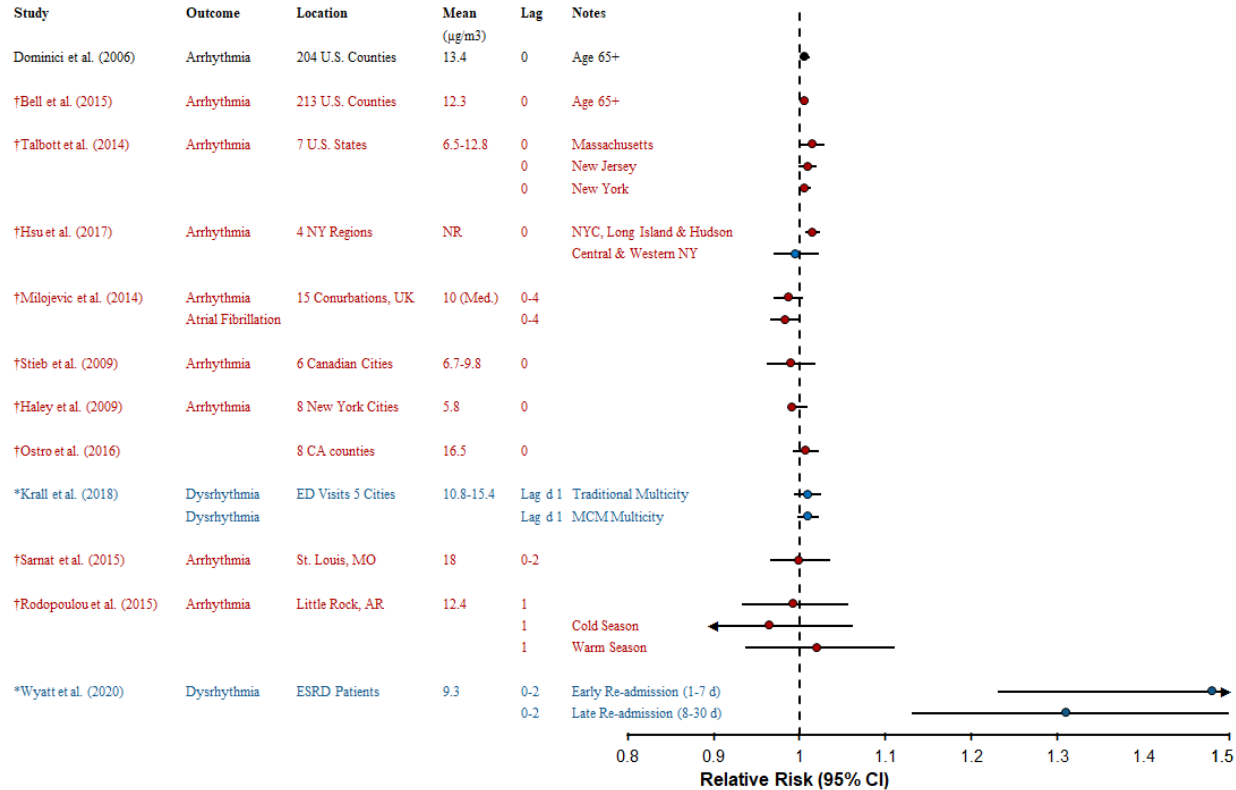
3.1.1.2.5. Combinations of Cardiovascular-Related Outcomes

In addition to analyses of individual CVDs (e.g., MI, stroke, and HF), epidemiologic studies examined CVDs in aggregate (i.e., specific combination of cardiovascular diseases). The 2009 PM ISA and the 2019 PM ISA reviewed multicity studies of adults ages 65 years and older that provided strong evidence of an association [(Bell et al., 2008; Host et al., 2008; Barnett et al., 2006); Table 6-19 of the 2019 PM ISA]. Studies of aggregate CVD have larger case counts than studies of specific CVDs, potentially providing statistical power needed to detect associations. Several recent studies examine the association between short-term exposure to $PM_{2.5}$ and CVD hospital admissions and ED visits, and report results that are generally consistent with studies evaluated in the 2019 PM ISA.

In a study of low-income and/or disabled Americans enrolled in Medicaid deSouza et al. (2021) estimated the association of $PM_{2.5}$ concentration (0−1 day average) with cardiovascular hospital admissions. The association of $PM_{2.5}$ concentration (0−1 day average) with all CVD hospital admissions was 1.09 (95% CI: 1.06, 1.11). In addition, the authors reported that the association with all CVD hospital admissions was larger in magnitude when restricting the analysis to $PM_{2.5}$ concentrations less than 25 micrograms per cubic meter ($\mu g/m^3$) (OR: 1.13 [95% CI: 1.09, 1.16]). The association was similar among older and younger adults (OR: 1.09 [95% CI: 1.06, 1.13]) among those < 65 years old 1.08 (95% CI: 1.06, 1.09) versus among those ≥ 65 years old. In another study, Wyatt et al. (2020c) examined hospital admissions among end-stage renal disease patients (i.e., those undergoing hemodialysis). Same-day $PM_{2.5}$ concentration (lag 0) was associated with an increase in the risk of CVD hospital admissions in this population (RR: 1.09 [95% CI: 1.02, 1.17]).

Some recent studies of ED visits report null associations between short-term $PM_{2.5}$ concentration and aggregated CVD outcomes in adjusted models. Krall et al. (2018) examined the associations of 24-hour $PM_{2.5}$ concentration (lag Day 0) with CVD ED visits, estimating the association across five cities using a traditional Bayesian hierarchical approach. A null association between 24-hour $PM_{2.5}$ concentration (lag 0) with CVD ED visits was observed (1.0 [95% CI: 0.992, 1.009]) while positive associations were reported for specific cardiovascular outcomes evaluated. Ye et al. (2018) performed a study to estimate the association between short-term exposure to $PM_{2.5}$ components that are not routinely measured, including water-soluble metals, and CVD ED visits for a five-county area of Atlanta during the period 1998 to 2013. In a single-pollutant model, these authors reported a positive association of 24-hour $PM_{2.5}$ concentration (lag 0) with CVD ED visits; however, the association was null after adjustment for water-soluble iron (WS Fe), which may be an indicator for certain aspects of traffic pollution.

Evidence assessed in the 2019 PM ISA from multicity studies reported consistent positive associations between short-term $PM_{2.5}$ exposure and cardiovascular-related ED visits and hospital admissions. Recent studies, including one in renal disease patients and another in the Medicaid population, support the conclusion of the 2019 PM ISA and extend the evidence base.

3.1.1.2.6.   Cardiovascular Mortality

As noted in the 2019 PM ISA, "studies that examine the association between short-term $PM_{2.5}$ exposure and cause-specific mortality outcomes, such as cardiovascular mortality, provide additional evidence for $PM_{2.5}$-related cardiovascular effects, specifically whether there is evidence of an overall continuum of effects" (2019 PM ISA, Section 6.1.9). Epidemiologic studies evaluated in the 2019 PM ISA, expanded upon the evidence presented in the 2009 PM ISA indicating consistent positive associations between short-term $PM_{2.5}$ exposure and cardiovascular mortality (2019 PM ISA, Section 6.1.9). Experimental evidence (i.e., both animal toxicological and controlled human exposure studies) presented within both the 2009 PM ISA and 2019 PM ISA provided coherence and biological plausibility for the $PM_{2.5}$-related cardiovascular mortality associations reported in epidemiologic studies. A recent multicity study conducted by Lavigne et al. (2018) in addition to examining short-term $PM_{2.5}$ exposure and total (nonaccidental) mortality also examined cause-specific mortality and provided evidence that continues to support a relationship between short-term $PM_{2.5}$ exposure and cardiovascular mortality (Section 3.2.1.2.2).

3.1.1.2.7.   Consideration of Copollutant Exposures

In the examination of potential confounding of the relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects by exposure to copollutants, it is informative to evaluate whether $PM_{2.5}$ risk estimates are changed in copollutant models. As noted in the Appendix (Table A-1) to the 2019 PM ISA, copollutant models are not without their limitations, such as instances for which correlations are high between pollutants resulting in greater bias in results. However, a change in the $PM_{2.5}$ risk estimate, after adjustment for a copollutant may indicate the potential for confounding. The evidence reviewed in the 2019 PM ISA represented an expanded set of studies that performed analyses using two-pollutant, also referred to as copollutant, models. These studies addressed a data gap, generally supporting an association of $PM_{2.5}$ with cardiovascular-related health effects that persisted after adjustment for copollutant exposures (i.e., O_3, NO_2, SO_2, CO, and $PM_{10-2.5}$). In addition to copollutant models, a limited number of studies that examined the joint effects of multiple pollutants provided information on the role of $PM_{2.5}$ within the complex air pollution mixture. Overall, the evidence and the available statistical methods were limited with respect to characterizing the multipollutant effects of air pollution on cardiovascular disease. This limited evidence neither consistently nor coherently indicated a stronger or weaker effect of combined exposure to $PM_{2.5}$ and another pollutant compared with exposure to a single pollutant alone (Luben et al., 2018).

Recent studies that examine the potential confounding of the relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects by copollutants are limited; however, the results of available studies are consistent with the evidence evaluated in the 2019 PM ISA. deSouza et al. (2021) found that the positive single-pollutant association (OR: 1.09 [95% CI: 1.06, 1.11]) between all CVD and short-term $PM_{2.5}$ observed among Medicaid recipients persisted in a two-pollutant model adjusted for ozone (OR: 1.10 [95% CI: 1.07, 1.12]). In another recent study, Wing et al. (2017) reported no association between

short-term $PM_{2.5}$ exposure and recurrent stroke in both single- and two-pollutant model that were adjusted for ozone. This study does not alter the conclusion of the 2019 PM ISA with respect to copollutant confounding because associations between $PM_{2.5}$ exposure and stroke were not consistently reported.

3.1.1.2.8.   Lag Structure of Associations

An examination of the association between short-term $PM_{2.5}$ exposure and cardiovascular effects across different lag days can inform whether $PM_{2.5}$ elicits an immediate (e.g., lag 0–1 days), delayed (e.g., lag 2–5 days), or prolonged (e.g., lag 0–5 days) effect on these endpoints, and whether the effect of $PM_{2.5}$ is consistent across cardiovascular endpoints. The evidence reviewed in the 2019 PM ISA supported an immediate effect of short-term $PM_{2.5}$ exposure on hospital admissions and ED visits for aggregate CVD outcomes, IHD, HF, and OHCA, as well as for cardiovascular mortality. This evidence came from the evaluation of both single-day and multiday lags, as well as studies that evaluated subdaily lag periods. By contrast, the studies evaluated in the 2019 PM ISA did not provide evidence of a consistent lag period for the association of short-term $PM_{2.5}$ exposure with CBVD and arrhythmia. Overall, stronger associations in terms of magnitude and precision were reported for immediate lags for most cardiovascular-related outcomes, and the associations tended to be stronger for immediate multiday lag periods (i.e., 0−1, 0−2) compared with immediate single-day lag periods (i.e., 0, 1).

Several recent studies conducted analyses to determine whether results were sensitive to the choice of exposure lag. Overall, the available studies continue to support an immediate effect of short-term $PM_{2.5}$ exposure on MI. In a case-crossover analysis of STEMI among unstable angina patients, Evans et al. (2017) found that the association between previous 1-hour $PM_{2.5}$ concentration and STEMI became less precise (i.e., wider confidence intervals) at exposure lags up to 24 or 48 hours and null with an exposure lag of 72 hours. In a multicity analysis of ED visits for a number of cardiovascular outcomes (i.e., IHD, CHF, Dysrhythmia), Krall et al. (2018) found that lags longer than their a priori choice (i.e., same-day exposure [lag 0]) did not produce substantially different results. Studies that examined the lag structure of associations in relation to stroke reported null associations that were unchanged regardless of the choice of lag (Fisher et al., 2019; McClure et al., 2017). In a study of recurrent IS in Nueces county Texas, Wing et al. (2017) reported null associations with short-term $PM_{2.5}$ concentrations on lag Day 1, 2, and 3 and an inverse association with same day exposures.

3.1.1.3.   Recent Epidemiologic Studies Examining the $PM_{2.5}$-Cardiovascular Effects Relationship through Accountability Analyses and Alternative Methods for Confounder Control

As discussed in Section 3.1.1.1, the 2019 PM ISA reported that there was sufficient evidence to conclude that a *causal relationship* exists between short-term $PM_{2.5}$ exposure and cardiovascular effects. However, the body of evidence that supported this causality determination did not include any

epidemiologic studies that conducted accountability analyses or employed alternative methods for confounder control because no such studies were published prior to the literature cutoff date for the 2019 PM ISA. Studies that conduct accountability analyses can provide insight on whether the implementation of environmental policies or air quality interventions result in changes/reductions in air pollution concentrations and the corresponding effect on health outcomes. Additionally, accountability studies can reduce uncertainties related to residual confounding of temporal and spatial factors. Alternative methods for confounder control seek to mimic randomized experiments through the use of study design and advanced statistical methods to reduce the potential bias of effects due to confounding more than traditional regression model approaches. Examples of alternative methods for confounder control are general propensity scores and inverse probability weighting models. Since the literature cutoff date for the 2019 PM ISA, several studies that conducted accountability analyses or implemented alternative methods for confounder control have been published, which further inform the relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects, specifically cardiovascular hospital admissions (Table A-2). The cardiovascular-related hospital admissions examined ranged from specific cardiovascular endpoints such cardiac arrhythmia, hypertension, ST segment elevation myocardial infarction to a broader assessment of all cardiovascular diseases.

Zhang et al. (2018) and Wang et al. (2019) both conducted accountability analyses that evaluated whether associations between short-term $PM_{2.5}$ exposures and cardiovascular hospital admissions differed before, during, and/or after the implementation of environmental policies to improve air quality in cities in New York. Zhang et al. (2018) estimated the rate of cardiovascular hospital admissions associated with short-term $PM_{2.5}$ concentrations, and whether the rates differed before (2005−2007), during (2008−2013), or after (2014−2016) the implementation of multiple national and state policies aimed at improving air quality in multiple cities in New York. Using a time-stratified, case-crossover design, the authors employed conditional logistic regression models to estimate the rate ratio for cardiovascular hospital admissions, examining associations with$PM_{2.5}$ at lag 0 or averaged over the previous 1–7 days (lag 0–1, 0–2, 0–3, 0–4, 0–5, 0−6), adjusting for temperature and relative humidity. The excess rate of hospital admissions decreased over the entire time period for total cardiovascular disease (before: 1.4% [95% CI: 1.0, 1.8]; during: 1.1% [95% CI: 0.7, 1.5]; after: 1.0% [95% CI: 0.3, 1.17]), with the largest association, in terms of magnitude, observed in the "before" implementation period and weaker associations observed in the "after" implementation period for the 0–6 day lag average. Similar results were reported for cerebrovascular disease, ischemic stroke, chronic rheumatic heart disease, hypertension, ischemic heart disease, and myocardial infarction. The incidence rates of all disease categories decreased across the study period. However, there was no difference in the excess rate of most cardiovascular disease subgroups associated with each interquartile range increase in $PM_{2.5}$ concentration "after" the implementation of environmental policies and actions (2014–2016) compared with "before" (2005–2007) or "during" (2008–2013) implementation. Conversely, there were increases in the excess rate of hospital admissions for cardiac arrhythmia and congestive heart failure in the "after" period compared with the "before" and "during" periods. Although the change in the excess rates for cause-specific cardiovascular hospital admissions was relatively small in magnitude and varied by lag period and location, overall,

short-term increases in ambient $PM_{2.5}$ concentrations were associated with increased rates of hospital admissions for total cardiovascular disease, cardiac arrhythmias, heart failure ischemic stroke, ischemic heart disease, and myocardial infarction.

Wang et al. (2019) also used a time-stratified case-crossover study design to examine whether the rate of ST segment elevation myocardial infarction (STEMI) is associated with $PM_{2.5}$ concentrations in the previous few hours or days, and whether these associations were modified by periods in which there were changes in environmental policies in Rochester, NY. The authors hypothesized that increases in the rate of STEMI associated with short-term $PM_{2.5}$ exposures would be smaller after the changes were implemented (2014−2016), compared with the periods before (2005−2007) and during (2008−2013) implementation. Within this study, referent days were selected as the same hour of the event on the same day earlier and later than the case event within the same month and calendar year. The analyses examined hourly exposures of 1 hour (lag hour 1), 3-hour avg (lag hours 0−2), 12-hour average (lag hours 0−11), 24-hour average (lag hours 0−23), 48-hour average (lag hours 0−47), and 72-hour average (lag hours 0−71) prior to the onset of STEMI symptoms. To examine whether the rate of STEMI was associated with different hourly average concentrations of $PM_{2.5}$ and were modified by the period of when changes were implemented, two interaction terms for the "period" (a categorical variable to distinguish periods of before, during, and after implementation) and $PM_{2.5}$ concentrations of the time period were included in the conditional logistic regression model. Over the entire study period, there was a decrease of approximately 30% in $PM_{2.5}$ concentrations. Across the three periods, there was a decrease in the rate of STEMI for an interquartile range (7.59 μg/m^3) increase in $PM_{2.5}$ concentration in the previous hour (lag hour 0) (before: OR = 1.03 [95% CI: 0.91, 1.17]; during: OR = 1.07 [95% CI: 0.92, 1.24]; after: OR = 0.99[95% CI: 0.81, 1.21]). However, in the previous 72-hour (lag hours 0−71) period, the rate of STEMI increased with an IQR increase in $PM_{2.5}$ concentration across the three periods from 0.91 (95% CI: 0.79, 1.05) before, 0.98 (95% CI: 0.82, 1.18) during, and 1.11 (95% CI: 0.88, 1.41) after implementation. Although the results of this accountability analysis are small in magnitude or null across the time periods, this study provides support that implementation of air quality policies can lead to reductions in $PM_{2.5}$ concentrations and subsequently may affect health effects associated with $PM_{2.5}$ exposures.

The use of alternative methods for confounder control can further inform the causal nature of the relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects through the use of advanced statistical methods to reduce uncertainties with respect to confounding. Recent epidemiologic studies that use these alternative methods have primarily focused on examining cardiovascular hospital admission rates. Inverse probability weighting (IPW) is an alternative method for confounder control that analyzes observational data in a way that approximates conducting a randomized experiment to make exposure independent of all potential confounders, rather than to control for the confounders in the outcome regression (Qiu et al., 2020). To explore the relationship between short-term $PM_{2.5}$ exposure and cardiovascular disease hospital admissions, Qiu et al. (2020) used IPW propensity score methods in a case-crossover study design to examine an unconstrained distributed lag (lag 0−5) for acute myocardial

infarction (AMI), CHF, and IS hospital admissions among New England Medicare participants between 2000 and 2012. In the first step, a linear regression model was fitted with the exposure lag of interest against the other five lags of $PM_{2.5}$ exposure and six lags of ozone along with linear and quadratic terms for temperature (lag 0 and 1) and linear terms for relative humidity (lag 0 and 1) to control for potential confounding by meteorological conditions. In the second step, under the assumptions that no important confounders are omitted and correct specification of the propensity score models, for each of the six lags the outcome was regressed against $PM_{2.5}$ at each individual lag with weights specific to each individual lag. After using the weights generated from propensity score models to predict the exposure at each lag of interest, copollutant exposure and meteorological variables were used to create a pseudo-randomized population. The pseudo-randomized population was subsequently used in conditional logistic regression models to regress cardiovascular hospital admissions against each exposure lag, estimating the marginal effect of each lag of exposure independent of covariates.

Using the IPW method, Qiu et al. (2020) reported an increase of 4.3% (95% CI: 2.2, 6.4) in AMI hospital admission rate, 3.9% (95% CI: 2.4, 5.5) in CHF rate, and 2.6% (95% CI: 0.4, 4.7) in IS hospital admission rate for a 10 μg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations. While Qiu et al. (2020) reported associations using alternative methods for confounder control that further confirm an association between short-term $PM_{2.5}$ exposure and cardiovascular-related hospital admissions, several assumptions were used by the authors when applying the IPW methods that are important to recognize. First, the authors assumed exchangeability, meaning that there was no unmeasured confounding, with the caveat that the authors did not have the resources to obtain all the potential unmeasured confounders. This assumption was tested through a series sensitivity analyses, testing the most critical confounder of temperature by including more lags of temperature and spline adjustments. Because the results from the sensitivity analyses involving temperature did not deviate from the estimates in the main analysis, it can be inferred that the most important confounders with available data were adjusted for and that the time-invariant variables are not potential confounders due to the case-crossover study design. The second assumption was positivity, which was guaranteed in the analysis through the positivity exclusion. Qiu et al. (2020) note that the positivity assumption means there are both exposed and non-exposed individuals at every level of the confounders. The last assumption is consistency, or that the observed outcome is exactly the same as the potential outcome the individual will have under the exposure assigned; however, this assumption is difficult to prove. Overall, the inverse probability weighted distributed lag model employed by Qiu et al. (2020) provides unconstrained, less conditional effect estimates that are less influenced by highly correlated covariates and reduces uncertainties regarding unmeasured confounders.

The recent studies that utilized accountability approaches and alternative methods for confounder control evaluated in this section provide additional support for a relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects. These studies reported consistent associations between cardiovascular hospital admissions with short-term $PM_{2.5}$ exposures across different statistical methods and study designs, which reduce uncertainties related to potential confounder bias, and further supports the conclusions of the 2019 PM ISA.

3.1.1.4. Summary of Recent Evidence in the Context of the 2019 Integrated Science Assessment for Particulate Matter Causality Determination for Short-Term PM$_{2.5}$ Exposure and Cardiovascular Effects

Recent epidemiologic studies published since the 2019 PM ISA support and extend the evidence that contributed to the conclusion of a *causal relationship* between short-term PM$_{2.5}$ exposure and cardiovascular effects in the 2019 PM ISA. Multicity analyses of the relationship between short-term exposure to PM$_{2.5}$ and cardiovascular ED visits and hospital admissions were an important consideration in this causality determination. Recent studies support the evidence characterized in the 2019 PM ISA, extending the evidence relating to hospital admissions and ED visits for specific outcomes (i.e., IHD, MI, HF, and arrhythmia) with positive association observed across diverse populations (i.e., older adults enrolled in Medicare, Medicaid recipients, and patient populations). With respect to stroke, the evidence in the 2019 PM ISA was characterized as inconsistent. Recent studies of established cohorts (i.e., WHI, REGARDS, and HPFU) extend this evidence with observations of null or inverse associations between short-term PM$_{2.5}$ exposure and stroke, regardless of stroke subtype. However, an association between short-term PM$_{2.5}$ exposure and IS was observed in the Medicaid population.

Multiple studies included in the 2019 PM ISA applied hybrid exposure assessment techniques that combined land use regression with satellite AOD measurements and PM$_{2.5}$ concentrations measured at fixed site monitors. Most recent studies also rely on exposure assessment strategies that characterize the temporal and spatial variability of short-term PM$_{2.5}$ concentrations. Recent studies also performed analyses to address methodological challenges, including applying techniques to elucidate uncertainties related to the observation of variable results across single-city studies and controlling for competing mortality risks in studies of ED visits and hospital admissions.

The evidence in the 2019 PM ISA indicated that the associations between short-term PM$_{2.5}$ exposure and cardiovascular effects generally persisted in models that were adjusted for copollutants. A recent study that reports copollutant model results supports the evidence characterized in the 2019 PM ISA that the effect of short-term PM$_{2.5}$ exposure on the cardiovascular system is independent of ozone exposure. Recent studies continue to support an immediate effect of short-term PM$_{2.5}$ exposure on the cardiovascular system that was described in the 2019 PM ISA. Finally, recent studies that employed alternative methods for confounder control or conducted accountability analyses when examining short-term PM$_{2.5}$ exposure and cardiovascular-related hospital admissions provide additional support for a relationship between short-term PM$_{2.5}$ exposure and cardiovascular effects while reducing uncertainties related to potential confounder bias.

3.1.2. Long-Term PM$_{2.5}$ Exposure

The following sections represent a summary of the evidence and the corresponding causality determination for long-term PM$_{2.5}$ exposure and cardiovascular morbidity presented within the 2019 PM

ISA ([Section 3.1.2.1](#)) along with an evaluation of recent epidemiologic studies that fall within the scope of the Supplement (i.e., studies conducted in the U.S. and Canada) and were published since the literature cutoff date of the 2019 PM ISA ([Section 3.1.2.2](#)). [15] In addition, with the expansion of epidemiologic studies that used statistical approaches that attempt to more extensively account for confounders and are more robust to model misspecification (i.e., used alternative methods for confounder control), recent studies that employed such methods are also evaluated ([Section 3.1.2.3](#)), which can further inform the relationship between long-term $PM_{2.5}$ exposure and cardiovascular morbidity. Finally, a summary of the results of recent studies evaluated within the section is presented in the context of the scientific conclusions detailed in the 2019 PM ISA ([Section 3.1.2.4](#)). The evaluation of recent studies presented in this Supplement adds to the collective body of evidence reviewed in the process of reconsidering the PM NAAQS.

3.1.2.1.   Summary and Causality Determination from 2019 Integrated Science Assessment for Particulate Matter

The evidence reviewed in the 2009 PM ISA provided the rationale to conclude that there is a "causal relationship between long-term $PM_{2.5}$ exposure and cardiovascular effects" ([U.S. EPA, 2009](#)). Studies of mortality from cardiovascular causes provided the strongest evidence in support of this conclusion. While several studies included in the 2009 PM ISA reported associations between long-term PM_{10} exposure and morbidity outcomes such as post-MI CHF and deep vein thrombosis (DVT), studies of $PM_{2.5}$ were limited. One large prospective study of postmenopausal women reported an increased risk of cardiovascular events, including CHD and stroke, in association with long-term exposure to $PM_{2.5}$ ([Miller et al., 2007](#)). Cross-sectional analyses provided supporting evidence and experimental studies demonstrating enhanced atherosclerotic plaque development and inflammation following long-term exposures to $PM_{2.5}$ CAPs provided biological plausibility for the epidemiologic findings. In addition, evidence from the limited number of toxicological studies reporting CAPs-induced effects on hypertension and vascular reactivity were drawn upon to support the causality determination.

In addition to evaluating evidence across scientific disciplines that examined the relationship between long-term $PM_{2.5}$ exposure and cardiovascular effects, the 2019 PM ISA characterized whether evidence supported biologically plausible mechanisms by which long-term $PM_{2.5}$ exposure could lead to cardiovascular effects. This evaluation consisted of an assessment of animal toxicological, controlled human exposure, and epidemiologic studies that examined a range of cardiovascular effects (2019 PM ISA, Section 6.2.1). Plausible biological mechanisms were identified by which inhalation exposure to $PM_{2.5}$ could progress from initial events to apical events reported in epidemiologic studies (2019 PM ISA, Figure 6-2). The first proposed pathway begins as respiratory tract inflammation leading to systemic

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[15] Throughout this section, as detailed in the Preface of the 2019 PM ISA (Section P.3.2.2), risk estimates from epidemiologic studies examining long-term exposures are for a 5 $\mu g/m^3$ increase in annual concentrations, unless otherwise noted.

inflammation. The second proposed pathway involves modulation of the autonomic nervous system. Once these pathways are initiated, there is evidence from experimental and observational studies that long-term exposure to $PM_{2.5}$ may result in a series of pathophysiological responses that could lead to cardiovascular events such as IHD and heart failure (2019 PM ISA, Figure 6-1).

The evidence for the relationship between long-term exposure to $PM_{2.5}$ and cardiovascular effects as characterized in the 2019 PM ISA is described below and summarized in Table 3-2, using the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015).

Table 3-2   **Summary of evidence for a *causal relationship* between long-term PM$_{2.5}$ exposure and cardiovascular effects from the 2019 Integrated Science Assessment for Particulate Matter.**

Rationale for Causality Determination[a]	Key Evidence[b]	Key References and Sections in the 2019 PM ISA[b]	PM$_{2.5}$ Concentrations Associated with Effects[c] ($\mu g/m^3$)
Consistent epidemiologic evidence from multiple studies at relevant PM$_{2.5}$ concentrations	Positive associations between long-term PM$_{2.5}$ exposure and cardiovascular mortality in U.S. and Canadian cohorts; positive associations persisted after adjustment for common confounders.	Section 6.2.10 Figure 6-19	Mean concentrations ranged from 4.08 (CCHS)−17.9 CA Teachers
	Positive associations observed in studies examining varying spatial scales and across different exposure assessment and statistical methods.	Section 6.2.10	
Evidence from copollutant models generally supports an independent PM$_{2.5}$ association	Positive associations observed between long-term PM$_{2.5}$ exposure and cardiovascular mortality remain relatively unchanged after adjustment for copollutants. Correlations with ozone were generally moderate to high (0.49−0.73). When reported, correlations with SO$_2$, NO$_2$, and PM$_{10-2.5}$ ranged from weak to moderate (r = 0.25−0.55).	Section 6.2.15 Figure 6-21 Figure 6-22	
Epidemiologic evidence supports a linear no-threshold C-R relationship	Most analyses support a linear, no-threshold relationship for cardiovascular mortality, especially at lower ambient concentrations of PM$_{2.5}$. Confidence in C-R relationship extends to 8 $\mu g/m^3$ in Harvard Six Cities study.	Section 6.2.16 Lepeule et al. (2012)	
Inconsistent evidence from epidemiologic studies of CHD or stroke	Association with coronary events, CHD, and stroke (mortality and morbidity combined) that persist after adjustment for SES reported in the WHI study. Association with stroke but not CHD in the CA Teachers cohort. No association with CHD or stroke in the NHS or HPFU.	Section 6.2.2 Section 6.2.3	Range: 13.4−17.8
Generally consistent evidence of an association with CHD or stroke among those with preexisting disease	Consistent associations with MI in patient populations. Association among women with diabetes in NHS.	Hartiala et al. (2016) Tonne et al. (2015) Koton et al. (2013) Hart et al. (2015b)	Mean: 15.5 Mean: 14.6 Mean: 23.9 Mean: 13.4

Rationale for Causality Determination[a]	Key Evidence[b]	Key References and Sections in the 2019 PM ISA[b]	PM$_{2.5}$ Concentrations Associated with Effects[c] (μg/m^3)
Some, but not all, epidemiologic studies provide evidence for effect of long-term PM$_{2.5}$ on CAC	Longitudinal change in CAC observed in MESA but not in Framingham Heart Offspring study.	Section 6.2.4 Kaufman et al. (2016) Dorans et al. (2016)	Mean: 14.2 Median: 9.8
Consistent evidence from animal toxicological studies at relevant PM$_{2.5}$ concentrations	Consistent changes in measures of impaired heart function and blood pressure. Additional evidence of atherosclerosis, systemic inflammation, changes in endothelial function.	Section 6.2.5.2 Section 6.2.7.2 Section 6.2.4.2 Section 6.2.12.2 Section 6.2.14.2	~85−30 See Tables in identified sections
Generally consistent evidence for biological plausibility of cardiovascular effects	Strong evidence for coherence of effects across scientific disciplines and biological plausibility for a range of cardiovascular effects in response to long-term PM$_{2.5}$ exposure. Includes evidence for impaired heart function, atherosclerosis, and increased blood pressure.	Section 6.2.1	

Note: This table corresponds to Table 6-54 in the 2019 PM ISA.

CAC = coronary artery calcification; CCHS = Canadian Community Health Survey; C-R = concentration-response; CHD = coronary heart disease; HPFU = Health Professionals Follow-Up; MESA = Multi-Ethnic Study of Atherosclerosis; μg/m^3 = micrograms per cubic meter; NHS = Nurses' Health Study; NO$_2$ = nitrogen dioxide; PM$_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm; PM$_{10}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 μm; PM$_{10-2.5}$ = particulate matter with a nominal mean aerodynamic diameter greater than 2.5 μm and less than or equal to 10 μm; r = correlation coefficient; SES = socioeconomic status; SO$_2$ = sulfur dioxide.

[a] Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble (U.S. EPA, 2015).

[b] Describes the key evidence and references contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described in the 2019 PM ISA.

[c] Describes the PM$_{2.5}$ concentrations with which the evidence is substantiated.

The studies of long-term exposure to $PM_{2.5}$ and cardiovascular mortality evaluated in the 2019 PM ISA continue to provide strong evidence of a *causal relationship* between long-term exposure to $PM_{2.5}$ and cardiovascular effects. Results from U.S. and Canadian cohort studies demonstrated consistent, positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality (2019 PM ISA, Figure 6-19). Overall, the studies reporting positive associations examined the relationship at varying spatial scales and employed different exposure assessment and statistical methods (2019 PM ISA, Section 6.2.10). The studies were conducted in locations where mean annual average concentrations ranged from 4.08 to 17.9 $\mu g/m^3$. Generally, most of the $PM_{2.5}$ effect estimates relating long-term $PM_{2.5}$ exposure and cardiovascular mortality remained relatively unchanged or increased in copollutant models adjusted for ozone, NO_2, $PM_{10-2.5}$, or SO_2. In addition, most of the results from analyses examining the C-R function for cardiovascular mortality supported a linear, no-threshold relationship for cardiovascular mortality, especially at lower ambient concentrations of $PM_{2.5}$.

The body of literature examining the relationship between long-term $PM_{2.5}$ exposure and cardiovascular morbidity evaluated in the 2019 PM ISA had greatly expanded since the 2009 PM ISA, with positive associations reported in several cohorts. The findings from the WHI cohort of postmenopausal women (Miller et al., 2007), reporting associations of long-term $PM_{2.5}$ and coronary events, were strengthened through a subsequent analysis, which considered potential confounding and modification by SES and applied enhanced exposure assessment methods (Chi et al., 2016). However, analyses of the Nurses' Health Study (NHS) and California Teachers Study (CTS), both of which are cohorts of women and include extensive data on covariates (i.e., hormone use, menopausal status, and SES), were not entirely consistent with the WHI findings. Although the NHS cohort is comparable to WHI in that it is made of predominantly postmenopausal women, no associations with CHD or stroke were observed in this population (Hart et al., 2015b). An association with stroke, but not CHD, that was stronger among postmenopausal women was observed in the CTS (Lipsett et al., 2011). Several studies conducted among cardiovascular disease patient populations generally reported positive associations with MI (Hartiala et al., 2016; Tonne et al., 2015; Koton et al., 2013), and a sensitivity analysis of the NHS restricted to women with diabetes detected a positive association with CHD. Although the evidence is not consistent across the populations studied, heterogeneity is expected when the methods, or the underlying distribution of covariates vary across studies (Higgins, 2008).

Longitudinal change in measures of atherosclerosis in relation to long-term exposure to $PM_{2.5}$ add to the collective evidence base (Hartiala et al., 2016; Kaufman et al., 2016; Gan et al., 2014; Künzli et al., 2010). Findings were somewhat variable across cohorts and depended, in part, on the vascular bed in which atherosclerosis was evaluated. Kaufman et al. (2016) reported an association of $PM_{2.5}$ with coronary artery calcification (CAC) among middle to older aged adults in the MESA study, while Dorans et al. (2016) reported no association in the Framingham Heart Study. Associations of long-term exposure to $PM_{2.5}$ with carotid intima media thickness (cIMT) were not consistently observed across cohorts or between analyses of the same cohort with variable methods. Relationships between $PM_{2.5}$ and cIMT at

younger ages were not observed. However, a toxicological study supported similar evidence from the 2009 PM ISA by demonstrating increased plaque progression in ApoE$^{-/-}$ mice following long-term exposure to PM$_{2.5}$ collected from multiple locations across the U.S. ([Lippmann et al., 2013a](#)). Thus, this study provided direct evidence that long-term exposure to PM$_{2.5}$ may result in atherosclerotic plaque progression. This study was also coherent with the epidemiologic studies discussed above reporting positive associations between long-term exposure to PM$_{2.5}$ and indicators of atherosclerosis.

A small number of epidemiologic studies also reported positive associations between long-term PM$_{2.5}$ exposure and heart failure (2019 PM ISA, Section 6.2.5), blood pressure, and hypertension (2019 PM ISA, Section 6.2.7). These heart failure studies are in agreement with animal toxicological studies that demonstrated decreased cardiac contractility and function and increased coronary artery wall thickness following long-term PM$_{2.5}$ exposure (2019 PM ISA, Section 6.2.5.2). Similarly, a limited number of animal toxicological studies demonstrated a relationship between long-term exposure to PM$_{2.5}$ and consistent increases in BP in rats and mice are coherent with epidemiologic studies that reported positive associations between long-term exposure to PM$_{2.5}$ and hypertension.

Longitudinal epidemiologic analyses also supported the observation of positive associations with markers of systemic inflammation (2019 PM ISA, Section 6.2.12), coagulation (2019 PM ISA, Section 6.2.13), and endothelial dysfunction (2019 PM ISA, Section 6.2.14). These results were in coherence with animal toxicological studies generally reporting increased markers of systemic inflammation and oxidative stress (2019 PM ISA, Section 6.2.12.2), as well as with toxicological studies that generally demonstrated endothelial dysfunction as evidenced by reduced vasodilation in response to acetylcholine (2019 PM ISA, Section 6.2.14).

There was also consistent evidence from multiple epidemiologic studies that long-term exposure to PM$_{2.5}$ was associated with mortality from cardiovascular causes. Associations with CHD, stroke, and atherosclerosis progression were observed in several additional epidemiologic studies, providing coherence with the mortality findings. Results from copollutant models generally supported the independence of the PM$_{2.5}$ associations. Additional evidence of the direct effect of PM$_{2.5}$ on the cardiovascular system was provided by experimental studies in animals, which in part, demonstrate biologically plausible pathways by which long-term inhalation exposure to PM$_{2.5}$ could potentially result in outcomes such as CHD, stroke, CHF, and cardiovascular mortality. **Together, these epidemiologic and experimental studies constitute strong evidence that a causal relationship exists between long-term exposure to PM$_{2.5}$ and cardiovascular effects.**

3.1.2.2.   Recent U.S. and Canadian Epidemiologic Studies

Recent epidemiologic studies conducted in the U.S. and Canada build upon the strong epidemiologic evidence base evaluated in the 2019 PM ISA, as well as in previous assessments, which provided the scientific rationale supporting a *causal relationship* between long-term PM$_{2.5}$ exposure and

cardiovascular effects (Section 3.1.1.1). In addition to examining the relationship between long-term PM$_{2.5}$ exposure and specific cardiovascular outcomes (i.e., IHD and myocardial infarction [Section 3.1.2.2.1], cerebrovascular disease and stroke [Section 3.1.2.2.2], atherosclerosis [Section 3.1.2.2.3], heart failure and impaired heart function [Section 3.1.2.2.4], cardiac electrophysiology and arrhythmia [Section 3.1.2.2.5], blood pressure and hypertension [Section 3.1.2.2.6], and cardiovascular mortality [Section 3.1.2.2.7]), analyses within these recent studies also further examined issues relevant to expanding the overall understanding the effect of long-term PM$_{2.5}$ exposure on cardiovascular outcomes. Specifically, recent studies assessed potential copollutant confounding (Section 3.1.2.2.8) and the shape of the concentration-response (C-R) relationship (Section 3.1.2.2.9). The following sections present an evaluation of recent epidemiologic studies conducted in the U.S. and Canada that inform each of the aforementioned topics within the context of the evidence base evaluated and summarized in the 2019 PM ISA. Study-specific details (e.g., study population, exposure assessment approach, confounders considered) for the epidemiologic studies evaluated in this section are presented in Appendix A (Table A-3).

3.1.2.2.1.   Ischemic Heart Disease and Myocardial Infarction

The terms ischemic heart disease (IHD), coronary artery disease (CAD), and coronary heart disease (CHD) are generally interchangeable as they appear in the epidemiologic literature on the effects of air pollution. Most IHD is caused by atherosclerosis, which can result in the blockage of the coronary arteries and restriction of blood flow to the heart muscle. A myocardial infarction (MI) or heart attack is an acute event that results in heart muscle tissue death secondary to coronary artery occlusion. The epidemiologic studies included in the 2019 PM ISA represented a substantial expansion of the literature compared with the few studies available for review in the 2009 PM ISA. Overall, findings from these studies were not entirely consistent. The strongest evidence of an association with IHD was found in populations with preexisting diseases such as diabetes or cardiac patients that are followed after an acute event or procedure. Recent studies examine the association between long-term PM$_{2.5}$ exposure and MI with most reporting results that are consistent with those studies evaluated in the 2019 PM ISA.

Recent analyses of the Canadian Ontario Population Health and Environment Cohort (ONPHEC) also add to the available evidence on the relationship between long-term PM$_{2.5}$ exposure and cardiovascular effects. ONPHEC includes more than 5 million Canadian-born adults (35−85 years old at enrollment in 1996) who were registered with the provincial health service and had resided in Ontario for ≥ 5 years. In a prospective analysis, Bai et al. (2019) estimated the association between 3-year average PM$_{2.5}$ concentrations and incident cases of acute MI. The study reported a positive association (HR: 1.07 [95% CI: 1.06, 1.09]). In addition, stratified analyses showed patterns of associations that indicated stronger effect estimates in the youngest (35−44 years) and oldest (75−85 years) age groups. Bai et al. (2019) also examined effect modification by oxidant gases, which was estimated as the redox weighted average of NO$_2$ and O$_3$ (O$_x$). A stronger association, in terms of magnitude, with acute MI was observed
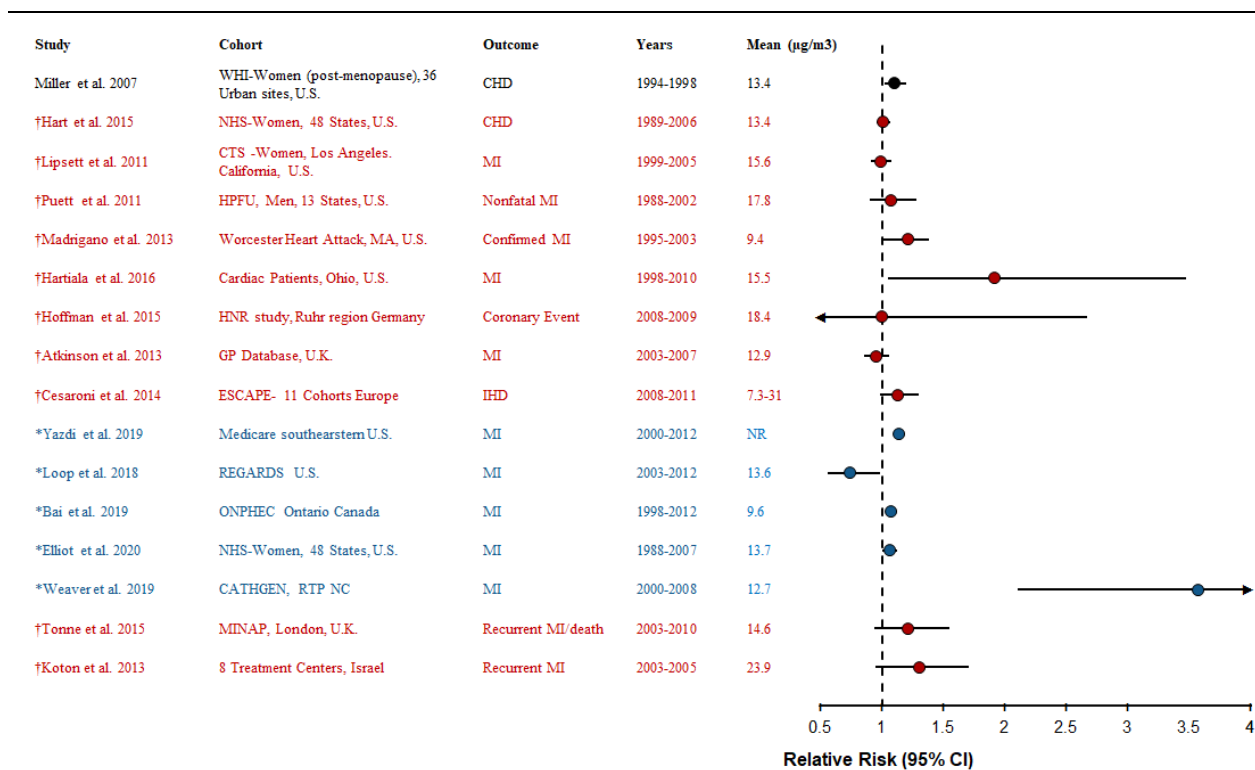
in the highest tertile of (> 38.97 ppm) O_x concentrations (HR: 1.12 [95% CI: 1.09, 1.15]) compared with the lowest (HR: 1.04 [95%CI: 1.01, 1.06]) and middle tertiles (HR: 1.06 [95% CI: 1.00, 1.12]).

Chen et al. (2020) also analyzed data from the ONPHEC study but examined the association of annual average $PM_{2.5}$ in the previous year with the incidence of acute MI. The authors conducted single pollutant analyses using both a traditional Cox proportional hazards model where $PM_{2.5}$ is fit as a linear term and a Cox proportional hazards model where $PM_{2.5}$ was fit as a nonlinear term. Model fit, which was assessed based on the Akaike information criterion (AIC) value, did not vary across models. The risk estimates were also virtually the same across models (i.e., HR = 1.14 [95% CI: 1.12, 1.16] in both models). In addition to conducting single-pollutant analyses, the authors introduced a new approach to assess whether the association of $PM_{2.5}$ with acute MI varied depending on the proportion of $PM_{2.5}$ attributed to selected components (i.e., sulfate, nitrate, ammonium, black carbon, organic matter, mineral dust, and sea salt). The study found that the model that adjusted for the proportion of each of the seven selected components was a better predictor of acute MI based on lower AIC values. In addition, Chen et al. (2020) reported that acute MI associations increased by an average of 10% when compared with single-pollutant results across each of the five regions of Ontario when using the component proportion adjusted approach. Overall, the component adjusted model provided some support that variability in the proportion of individual components that comprise $PM_{2.5}$, could explain regional variability in risk estimates.

While the studies above focus on examining the relationship between long-term $PM_{2.5}$ exposure and MI in cohorts of diverse populations, some recent studies have analyzed data from a cohort of women and cardiac catheterization patients. Elliott et al. (2020) examined the interaction between 24-month $PM_{2.5}$ concentration and physical activity in association with MI among women enrolled in the NHS. Unlike an earlier analysis of this cohort that examined IHD (Hart et al., 2015b), the authors found a positive association of $PM_{2.5}$ with MI (HR: 1.06 [95% CI: 1.00, 1.12]), although no statistical evidence of an interaction with physical activity was observed. In the previous analysis of the NHS cohort, Hart et al. (2015b) reported no association between long-term $PM_{2.5}$ exposure and incident CHD (HR: 1.01 [95% CI: 0.96, 1.07]), although a positive association with IHD was observed among women with diabetes (HR: 1.10 [95% CI: 0.99, 1.21]). Weaver et al. (2019) studied cardiac catheterization patients residing in three counties in NC to determine the association of annual average $PM_{2.5}$ concentration with MI, CAD, and hypertension. Among the objectives of this study was to understand the effect of sociodemographic characteristics on associations by assigning study participants to clusters based on the census block group of their residence that indicated specific sets of sociodemographic characteristics. Positive associations of annual average $PM_{2.5}$ concentration with both CAD and MI were observed. The association with MI was observed across all sociodemographic clusters (OR for all clusters: 3.57 [95% CI: 2.10, 5.77]). The association with CAD was also observed across all clusters (OR: 1.40 [95% CI: 0.90, 2.19]) but was largely driven by one cluster (OR: 2.01 [95% CI: 1.00, 3.86]), which was urban and characterized by low poverty, low unemployment, and composed of relatively highly educated residents with managerial jobs.

In another study, Loop et al. (2018) conducted an analysis of the REGARDS cohort, a nationwide study which oversampled participants from states in the southern U.S. where there is known to be an increased risk of stroke. Participants who were free from CHD at baseline were followed for an average of 6 years. Loop et al. (2018) reported an inverse association between annual average PM$_{2.5}$ concentration at baseline and nonfatal MI (HR: 0.74 [95% CI: 0.56, 0.98]). Loop et al. (2018) also examined associations for total CHD (i.e., CHD deaths and nonfatal MI cases combined) and reported no evidence of an association (HR: 0.89 [95% CI: 0.71, 1.11]).

The evidence informing the relationship between long-term exposure to PM$_{2.5}$ and IHD, including the recent studies of MI, is summarized in Figure 3-5. Recent studies do not all report positive associations; however, the strongest evidence of a relationship continues to be for those with preexisting diseases or patient populations that are followed after a cardiac event or procedure such as catheterization.

Study	Cohort	Outcome	Years	Mean (µg/m3)
Miller et al. 2007	WHI-Women (post-menopause), 36 Urban sites, U.S.	CHD	1994-1998	13.4
†Hart et al. 2015	NHS-Women, 48 States, U.S.	CHD	1989-2006	13.4
†Lipsett et al. 2011	CTS -Women, Los Angeles. California, U.S.	MI	1999-2005	15.6
†Puett et al. 2011	HPFU, Men, 13 States, U.S.	Nonfatal MI	1988-2002	17.8
†Madrigano et al. 2013	Worcester Heart Attack, MA, U.S.	Confirmed MI	1995-2003	9.4
†Hartiala et al. 2016	Cardiac Patients, Ohio, U.S.	MI	1998-2010	15.5
†Hoffman et al. 2015	HNR study, Ruhr region Germany	Coronary Event	2008-2009	18.4
†Atkinson et al. 2013	GP Database, U.K.	MI	2003-2007	12.9
†Cesaroni et al. 2014	ESCAPE- 11 Cohorts Europe	IHD	2008-2011	7.3-31
*Yazdi et al. 2019	Medicare southeastern U.S.	MI	2000-2012	NR
*Loop et al. 2018	REGARDS U.S.	MI	2003-2012	13.6
*Bai et al. 2019	ONPHEC Ontario Canada	MI	1998-2012	9.6
*Elliot et al. 2020	NHS-Women, 48 States, U.S.	MI	1988-2007	13.7
*Weaver et al. 2019	CATHGEN, RTP NC	MI	2000-2008	12.7
†Tonne et al. 2015	MINAP, London, U.K.	Recurrent MI/death	2003-2010	14.6
†Koton et al. 2013	8 Treatment Centers, Israel	Recurrent MI	2003-2005	23.9

Source: Update of Figure 6-17, 2019 PM ISA.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent evidence considered in 2019 PM ISAs; and blue text and circles represent recent studies published since the 2019 ISA. Mean concentrations in $µg/m^3$. Hazard ratios are standardized to a 5 $µg/m^3$ increase in $PM_{2.5}$ concentrations. CATHGEN = Catheterization Genetics Study; CHD = Coronary Heart Disease; CTS = California Teachers Study; ESCAPE = European Study of Cohorts for Air Pollution; HNR = Heinz Nixdorf Recall study; HPFU = Health Professionals Follow-up Study; IHD = Ischemic Heart Disease; MI = myocardial infarction; MINAP = Myocardial Ischemia National Audit Project; NHS = Nurses' Health Study; ONPHEC = Ontario Population Health and Environmental Cohort; REGARDS = REasons for Geographic and Racial Differences in Stroke; WHI = Women's Health Initiative.

Figure 3-5   Associations between long-term PM$_{2.5}$ exposure and ischemic heart disease or myocardial infarction.

3.1.2.2.2.   Cerebrovascular Disease and Stroke

Cerebrovascular disease typically includes the conditions hemorrhagic stroke, cerebral infarction (i.e., ischemic stroke), and occlusion of the precerebral and cerebral arteries. The 2009 PM ISA identified one study that indicated a positive association between $PM_{2.5}$ and cerebrovascular morbidity and mortality (HR: 1.16 [95%CI: 1.04, 1.30]) in post-menopausal women (Miller et al., 2007). Although the results were not entirely consistent across studies or stroke subtype, some studies reviewed in the 2019 PM ISA provided evidence to support a positive association between long-term exposure to $PM_{2.5}$ and stroke. Several recent studies that observe positive associations add to this evidence base (Figure 3-6).

Several studies examined the association between long-term $PM_{2.5}$ concentration and stroke as discussed below. In a study of women enrolled in the NHS cohort, Elliott et al. (2020) reported an imprecise (i.e., wide confidence intervals relative to the size of the HR) association between 24 month average $PM_{2.5}$ concentration and stroke that overlapped the null value (HR: 1.02 [95% CI: 0.96, 1.09]). An earlier analysis examining the association with annual average $PM_{2.5}$ concentration in the NHS, reported an increased risk among women with diabetes (HR: 1.29 [95% CI: 1.14, 1.45]) but not in the population, overall (HR: 1.01 [95% CI: 0.96, 1.05]) (Hart et al., 2015b). Rhinehart et al. (2020) estimated the association of annual average $PM_{2.5}$ concentration within 300 meters of the residence with stroke in a prospective analysis of residents of Allegheny County, PA, who were diagnosed with atrial fibrillation but had no history of stroke. This study reported a positive association (HR: 1.62 [95% CI: 1.00, 2.55]). As opposed to examining annual or 24-month average $PM_{2.5}$ exposures, Shin et al. (2019) estimated the association between 5-year $PM_{2.5}$ concentration and incident cases of stroke in a prospective analysis of the Canadian ONPHEC study and reported a positive association (HR: 1.05 [95% CI: 1.03, 1.07]).

Studies that examined the relationship of long-term $PM_{2.5}$ exposure with CBVD and stroke are summarized in Figure 3-6. Recent studies support the evidence in the 2019 PM ISA and extend the evidence relating to the observation of associations among patients that are followed after a cardiac event or procedure.

Study	Cohort	Outcome	Years	Mean (µg/m3)
Miller et al. 2007	WHI-Women (post-menopause) 36 Urban Sites, US	Stroke	1994-1998	13.4
†Hart et al. 2015	NHS- Women, 48 States, U.S.	Stroke	1989-2006	13.4
*Elliot et al. 2020	NHS- Women, 48 States, U.S.	Stroke	1988-2007	13.7
†Lipsett et al. 2011	CTS -Women, Los Angeles, California, U.S.	Stroke	1999-2005	15.6
†Puett et al. 2011	HPFU, Men, 13 States, U.S.	IS	1988-2002	17.8
†Puett et al. 2011	HPFU, Men, 13 States, U.S.	HS	1988-2002	17.8
*Yazdi et al. 2019	Medicare U.S.	1st Admission Stroke	2000-2012	NR
*Shin et al. 2019	ONPHEC, Ontario Canada	1st Admission Stroke	1998-2012	9,8
*Rhinehart et al. 2020	Atrial Fibrillation Patients, U.S.	IS	2007-20017	10.6
†Hartiala et al. 2016	Cardiac Patients, Ohio, U.S.	Stroke	1998-2010	15.5
†Stafoggia et al. 2014	ESCAPE- 11 Cohorts Europe	Stroke	2008-2011	7.3-31
†Hoffmann et al. 2015	HNR study, Ruhr area, Germany	Stroke	2008-2009	18.4
†Atkinson et al. 2013	GP Database, U.K.	Stroke	2003-2007	12.9
†Koton et al. 2013	8 Centers, Israel	Post MI Stroke	2003-2005	23.9

Relative Risk (95% CI)

Source: Update of Figure 6-18, 2019 PM ISA.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent evidence included in the 2019 PM ISA; blue text and circles represent evidence not included in the 2019 PM ISA. Mean concentrations in $\mu g/m^3$. Hazard ratios are standardized to a 5 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations. (U.S. EPA, 2018). ESCAPE = European Study of Cohorts for Air Pollution; GP = general practitioner; HNR = Heinz Nixdorf Recall; HPFU = Health Professional's Follow-up; HS = hemorrhagic stroke; IS = ischemic stroke; MI = myocardial infarction; NHS = Nurses' Health Study; ONPHEC = Ontario Population Health and Environment Cohort; WHI = Women's Health Initiative.

Figure 3-6   Associations between long-term PM2.5 exposure and the incidence of stroke.

3.1.2.2.3.   Atherosclerosis

Atherosclerosis is the process of plaque buildup that forms lesions on the walls of the coronary arteries, which can lead to narrowing of the vessel, reduced blood flow to the heart and IHD. Atherosclerosis can be assessed within large arterial vascular beds in distinct regions of the body i.e., carotid intima-media thickness (cIMT), coronary artery calcification (CAC), ankle-brachial index (ABI), and the presence of plaques. Findings from studies reviewed in the 2009 PM ISA were inconsistent, reporting null or positive, but imprecise associations with cIMT, CAC, and ABI. Similarly, findings from studies reviewed in the 2019 PM ISA were not entirely consistent across populations, exposure assessment methods, and measures of atherosclerosis. Notably, an extended MESA analysis reported a longitudinal increase in CAC (4.1 Agatston unit increase per year [95% CI: 1.4, 6.8]) in association with annual average $PM_{2.5}$ exposure, but no association (β: -0.90 µm per year [95%CI: -3.00,

1.30]) with cIMT (Kaufman et al., 2016). Exposure measurement error, variation in baseline measures of atherosclerosis as well as statistical power were noted as possible explanations for the lack of association observed in these studies. Consideration of copollutant confounding was generally limited across the evidence base reviewed in the 2019 PM ISA.

Several recent studies expand the evidence available to consider the association of long-term $PM_{2.5}$ exposure with atherosclerosis. Following the analysis by Kaufman et al. (2016), Keller et al. (2018) estimated the association of $PM_{2.5}$ concentration (i.e., multi-year average during the study period 2000−2012) with CAC progression among participants in MESA air residing in Baltimore, MD. The authors also assessed whether this association was modified by membership in clusters with different traffic-related air pollution (TRAP) component profiles. The authors reported a 23.0 Agatston unit per year increase (95% CI :14.2, 31.7) among participants overall. Keller et al. (2018) also reported a larger magnitude association with CAC progression (42.6 Agatston unit per year increase [95% CI: 25.7, 59.4]) in the cold season among those belonging to a cluster that was characterized as downtown with above average ratios of ultrafine and accumulation mode particles relative to NO_X.

Among women enrolled in the Study of Women's Health Across the Nation (SWAN), a cohort of U.S. women transitioning through menopause, Duan et al. (2019a) estimated the association of 5-year average $PM_{2.5}$ concentration with cIMT. The study reported a 27.95 μm (95% CI: −2.90, 58.75) thicker mean cIMT in association with 5-year mean $PM_{2.5}$ concentration in adjusted models. $PM_{2.5}$ was also associated with an increase in increased mean inter-adventitial diameter (IAD), which is a marker of vascular remodeling and aging as well as a predictor of cardiovascular events, of 105.90 (95% CI: −63.00, 274.80). No association was reported with plaque presence (OR: 0.90 [95% CI: 0.50, 1.61]) or plaque severity index (plaque index 0−2, OR: 1.05 [95% CI: 0.53, 8.95] and plaque index > 2, OR: 0.62 [95% CI: 0.25, 1.47]) in the SWAN study. In an analysis of a subset of SWAN participants (Pittsburgh and Chicago only), Duan et al. (2019b) estimated the association of the same measures of atherosclerosis as Duan et al. (2019a) with annual average $PM_{2.5}$ concentration reporting a 11.25 μm per year increase (95% CI: −3.05, 25.60) in mean cIMT. The authors also reported associations with plaque presence (OR: 2.10 [95% CI: 0.66, 6.63]) and plaque index progression (OR: 2.70 [95% CI: 0.77, 9.24]).

Recent studies support and extend the evidence characterized in the 2019 PM ISA with observations of associations with cIMT among women transitioning into menopause and potential effect modification by TRAP in the MESA study.

3.1.2.2.4.   Heart Failure and Impaired Heart Function

HF refers to a set of conditions including CHF in which the heart's pumping action is weakened. With CHF the blood flow from the heart slows, failing to meet the oxygen demands of the body, and returning blood can back up, causing swelling or edema in the lungs or other tissues (typically in the legs and ankles). Risk factors for HF include IHD, high blood pressure, atrial fibrillation, and diabetes. The

small number of epidemiologic studies reviewed in the 2019 PM ISA provided evidence supporting a possible relationship between heart failure and long-term exposure to $PM_{2.5}$. In addition, an association with increased right ventricular (RV) mass was observed among MESA participants (Aaron et al., 2016). Right sided HF is typically a consequence of left-sided HF but can also result from damage to the pulmonary vasculature, which can result in increased RV mass, reduced flow to the left ventricle, and reduced left ventricular (LV) mass.

A recent study examining the association between long-term $PM_{2.5}$ exposure and HF was conducted among participants in the Canadian ONPHEC study. In this prospective analysis, Bai et al. (2019) examined the relationship between 3-year moving average $PM_{2.5}$ concentration with new cases of CHF. A positive association was reported, overall (HR: 1.07 [95% CI: 1.06, 1.07]), and a larger magnitude association was reported in the highest tertile of O_x concentrations in a stratified analysis examining potential effect modification (HR: 1.12 [95% CI: 1.10, 1.13]). The hazard ratios in the lowest and middle O_x tertiles were 1.04 (95% CI: 1.03, 1.06) and 1.06 (95% CI: 1.03, 1.07), respectively. This study supports the evidence in the 2019 PM ISA that indicates a positive association between long-term $PM_{2.5}$ and HF; however, the evidence remains limited overall.

3.1.2.2.5.   Cardiac Electrophysiology and Arrhythmia

Electrical activity in the heart is typically measured using surface electrocardiography (ECG). ECGs measure electrical activity in the heart due to depolarization and repolarization of the atria and ventricles. Atrial fibrillation (AF) is the most common type of arrhythmia. Despite being common, clinical and subclinical forms of AF are associated with reduced functional status and quality of life and are associated with downstream consequences such as ischemic stroke (Prystowsky et al., 1996; Laupacis et al., 1994) and CHF (Roy et al., 2009), contributing to both CVD and all-cause mortality (Kannel et al., 1983). Ventricular fibrillation is a well-known cause of sudden cardiac death and commonly associated with MI, HF, cardiomyopathy, and other forms of structural (e.g., valvular) heart disease.

In an analysis of the WHI, which was reviewed in the 2009 PM ISA, Liao et al. (2009) found no association of long-term $PM_{2.5}$ concentrations with supraventricular or ventricular ectopy, which are the most frequent forms of arrhythmia in the general population. A limited number of studies reviewed in the 2019 PM ISA found associations of long-term $PM_{2.5}$ exposure with premature atrial contractions and ventricular conduction abnormalities, but not arrhythmias recorded on implantable cardioverter defibrillators. In a recent prospective analysis of the Canadian OPHEC study, Shin et al. (2019) estimated the association between 5-year average $PM_{2.5}$ concentration and incident cases of AF and reported a positive association (HR: 1.03 [95% CI: 1.01, 1.04]). Overall, the evidence pertaining to the association between long-term $PM_{2.5}$ exposure and various types of arrythmias remains limited.

3.1.2.2.6.   Blood Pressure and Hypertension

High blood pressure is typically defined as a systolic blood pressure above 140 mm Hg or a diastolic blood pressure above 90 mm Hg (U.S. EPA, 2019). Hypertension, the clinically relevant consequence of chronically high blood pressure, typically develops over years. The body of literature reviewed in the 2019 PM ISA was substantially larger than in the 2009 PM ISA with longitudinal analyses generally showing small magnitude increases in SBP, pulse pressure (PP), and mean arterial pressure (MAP) in association with long-term exposure to $PM_{2.5}$. In addition, the expanded body of literature provided evidence of associations between long-term $PM_{2.5}$ exposure and hypertension. Recent studies add to the evidence providing support for positive associations among post-menopausal women enrolled in the WHI study and in cardiac catheterization patients, but not among Black women enrolled in the Jackson Heart Study (JHS).

Honda et al. (2017) estimated the association of $PM_{2.5}$ concentration with incident hypertension among post-menopausal women enrolled in the WHI. Annual average $PM_{2.5}$ concentration was associated with incident hypertension. (HR: 1.17 [95% CI 1.10, 1.22]). The association with $PM_{2.5}$ concentration increased among minority participants (i.e., Black, Asian/Pacific Islander, Hispanic/Latino race/ethnicity, which were characterized as non-White in the study) participants and those who lived in the Northeast U.S. By contrast, no association of 1-year or 3-year average $PM_{2.5}$ concentration with hypertension was observed in a recent prospective analysis conducted by Weaver et al. (2021) of African American women enrolled in the JHS (1-year, RR: 1.00 [95% CI: 0.52, 2.03] and 3-year, RR: 1.10 [95% CI: 0.39, 2.84]). Further adjustment for diabetes did not change these findings. A cross-sectional analysis of $PM_{2.5}$ concentration and prevalent hypertension conducted by Weaver et al. (2021) yielded similar results.

An association between long-term $PM_{2.5}$ exposure and hypertension was also observed among cardiac catheterization patients in three counties in North Carolina (Weaver et al., 2019). In this study Weaver et al. (2019) estimated the association of annual average $PM_{2.5}$ concentration with hypertension. No association between long-term $PM_{2.5}$ exposure and hypertension was observed in the study population overall (OR: 0.90 [95% CI: 0.59, 1.34). The pattern of associations between long-term $PM_{2.5}$ concentration and hypertension indicated larger magnitude associations among study participants who lived in two sociodemographic clusters, the first characterized as urban, having a high proportion of Black individuals and individuals in non-managerial occupations (denoted as Cluster 1) and the second characterized as urban, impoverished, having a high proportion of individuals who are unemployed, work in non-managerial occupations, are Black, and live in single parent homes (Cluster 2). The OR for Cluster 1 was 2.70 (95% CI: 0.95, 7.59) and the OR for Cluster 2 was 11.86 (95% CI: 2.10, 67.21).

The literature assessed in the 2019 PM ISA provided evidence of associations between long-term $PM_{2.5}$ exposure and hypertension. Recent studies are generally consistent with this assessment, reporting positive associations among post-menopausal women enrolled in the WHI study and in cardiac catheterization patients. However, no association between long-term $PM_{2.5}$ exposure and hypertension was observed among Black women enrolled in the JHS.

3.1.2.2.7.   Cardiovascular Mortality

Multiple epidemiologic studies (Section 3.2.2.2.2) reviewed in the 2009 PM ISA and in the 2019 PM ISA reported consistent positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality. Generally, these studies had extensive control for a wide range of potential confounders and the observed effect estimates remained relatively unchanged or increased in copollutant models adjusted for ozone, NO_2, $PM_{10–2.5}$, or SO_2. Recent cohort studies, which are reviewed in detail in Section 3.2.2.2.2 provide additional evidence for associations with cardiovascular mortality outcomes across the distribution of $PM_{2.5}$ concentrations (Hayes et al., 2020), the potential implications of a comorbidity on the $PM_{2.5}$-cardiovascular mortality relationship (Pinault et al., 2018), and associations with individual cardiovascular mortality outcomes including IHD (Crouse et al., 2020; Wang et al., 2020; Cakmak et al., 2018; Pinault et al., 2017) and stroke (Crouse et al., 2020; Hayes et al., 2020; Wang et al., 2020; Pope et al., 2019; Pinault et al., 2017). Overall, these recent studies support the conclusions in the 2019 PM ISA of consistent positive associations of long-term $PM_{2.5}$ exposure with cardiovascular mortality, and specifically with IHD- and stroke-related mortality. Although Pope et al. (2014) reported positive associations of long-term $PM_{2.5}$ exposure with CHF mortality in a study of the ACS cohort evaluated in the 2019 PM ISA, a recent analysis of the Medicare cohort Wang et al. (2020) reported a null association. Recent studies also indicate that the combination of cardiovascular disease and diabetes together has a greater mortality risk than cardiovascular mortality alone and that cardiovascular diseases such as heart failure or previous MI may increase the risk of $PM_{2.5}$-related all-cause mortality (Ward-Caviness et al., 2020; Malik et al., 2019).

3.1.2.2.8.   Copollutant Confounding

One approach to assessing the independence of the association between exposure to $PM_{2.5}$ and a health effect, such as long-term exposure to $PM_{2.5}$ and cardiovascular health effects is through the use of copollutant models. As noted in the Appendix (Table A-3) to the 2019 PM ISA, copollutant models are not without their limitations, such as instances when correlations are high between pollutants resulting in greater bias in results. However, in assessing the results from copollutant models, a change in the $PM_{2.5}$ risk estimates, after adjusting for copollutants, may indicate the potential for confounding. A limited number of studies were available in the 2019 PM ISA to assess copollutant confounding of the association between long-term exposure to $PM_{2.5}$ and cardiovascular morbidity. Considering these few available studies, risk estimates remained largely unchanged after adjustment for $PM_{10–2.5}$, NO_2, and $PM_{2.5}$ from traffic sources. The limited number of recent analyses report some attenuation of risk estimates in models adjusted for O_3 and NO_2.

Several recent analyses of the ONPHEC study add to the evidence pertaining to copollutant confounding (Figure 3-7). Shin et al. (2019) reported that the association of long-term $PM_{2.5}$ exposure with stroke (HR: 1.03 [95%CI: 1.01, 1.04]) persisted after adjustment for NO_2 but was attenuated in the

models with O_3 and oxidant gases (O_x) represented by the redox weighted average of NO_2 and O_3 (HR: 1.05 [95% CI: 1.03, 1.06] and HR: 1.03 [95% CI:1.02, 1.04], and HR: 1.02 [95% CI:1.00, 1.05], respectively). In an analysis of AF, these authors found that the association was slightly attenuated, but remained positive, in two-pollutant models that adjusted for NO_2, O_3 and redox weighted average of NO_2 and O_3 (O_x) (HR: 1.03 [95% CI: 1.02, 1.04] and HR: 1.02 [95% CI: 1.01, 1.03], and HR: 1.02 [95% CI: 1.01, 1.03], respectively). In addition, a study of atherosclerosis in the SWAN cohort, Duan et al. (2019a) reported that the estimate for the association of long-term $PM_{2.5}$ exposure with cIMT was slightly attenuated in a two-pollutant model that adjusted for O_3 (24.45 μm [95% CI: −18.35, 67.25]). In a separate analysis of a subset of this cohort, however, Duan et al. (2019b) reported that associations with plaque presence and plaque index progression persisted in models adjusted for ozone (OR: 2.29 [95% CI: 0.70, 7.59]) for plaque presence and (OR 3.05 [95% CI: 0.86, 10.82] for plaque index progression). Overall, the limited evidence indicates that associations between $PM_{2.5}$ and cardiovascular health effects persist, but may be slightly attenuated, in models that are adjusted for copollutants.
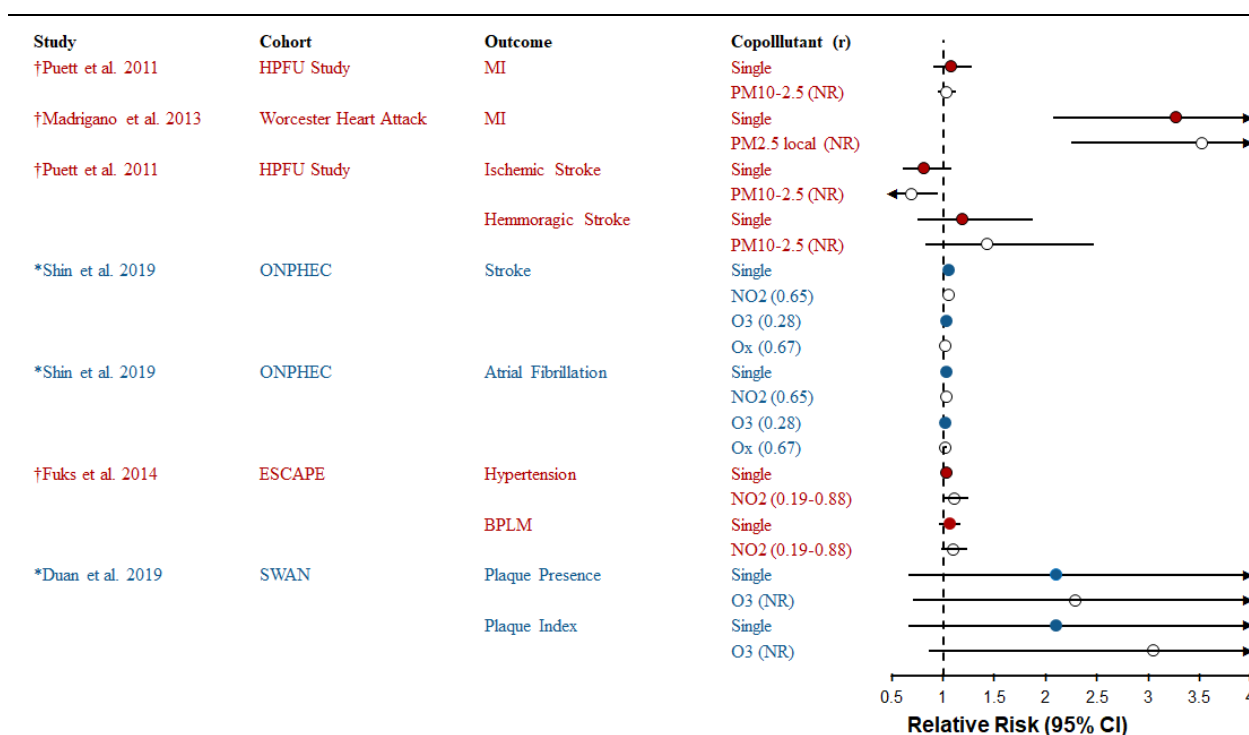
Source: Update of Figure 6-20, 2019 PM ISA.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for 2019 PM ISA. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Solid circles represent single pollutant results and open circles represent copollutant results. Hazard ratios are standardized to a 5 μg/m^3 increase in $PM_{2.5}$ concentrations.

Figure 3-7   **Associations between long-term exposure to PM2.5 and cardiovascular morbidity in single pollutant models and models adjusted for copollutants.**

3.1.2.2.9.   Examination of the Concentration-Response (C-R) Relationship between Long-Term PM$_{2.5}$ Exposure and Cardiovascular Effects

An important consideration in characterizing the association between long-term PM$_{2.5}$ exposure and cardiovascular effects is whether the C-R relationship is linear across the full concentration range that is encountered, or whether there are concentration ranges that exhibit departures from linearity. A limited number of studies evaluated in the 2019 PM ISA examined the shape of the C-R relationships for cardiovascular morbidity outcomes with the majority of studies lacking thorough evaluations of alternatives to linearity (2019 PM ISA, Table 6-51). Several recent studies expand the evidence pertaining to the shape of the C-R relationship for the incidence of MI, AF, stroke, and CHF. A number of these studies use statistical techniques that allow for departures from linearity (Table 3-3) generally supporting and extending the evidence characterized in the 2019 PM ISA showing linear, no-threshold C-R relationship for most CVD outcomes. However, there is some evidence for a sublinear or supralinear C-R relationship for some outcomes.

Table 3-3   Summary of studies examining the concentration-response (C-R) relationship or conducted threshold analyses for long-term exposure to PM$_{2.5}$ and cardiovascular morbidity.

Study Location—Cohort (Table/Figure from Reference)	Outcome	Exposure PM$_{2.5}$ Mean: (Range) in µg/m³	Statistical Analysis Summary
Bai et al. (2019) Figure 3-8 Ontario, Canada ONPHEC	Acute MI incidence	Mean (IQR):9.6 (3.5)	Identified the shape of the C-R function for fully adjusted Cox models using SCHIF** (Nasari et al., 2016). A linear concentration-response relationship between acute MI and PM$_{2.5}$ concentration was observed.
Chen et al. (2020) Figure 3-9 Ontario, Canada ONPHEC	Acute MI Incidence	Mean: 8.61	Identified the shape of the C-R function for fully adjusted Cox models using SCHIF** (Nasari et al., 2016). Restricted cubic splines with 4 df to assess linearity used in sensitivity analysis. Approximately linear relationship observed with both methods.
Danesh Yazdi et al. (2019) Figure 3-10 Medicare Southeastern, U.S.	First hospital admission for MI	NR	Penalized spline to estimate the shape of the C-R relationship, with degrees of freedom chosen based on corrected AIC values.

Table 3-3 (Continued): Summary of studies examining the concentration-response (C-R) relationship or conducted threshold analyses for long-term exposure to PM$_{2.5}$ and cardiovascular morbidity.

Study Location—Cohort (Table/Figure from Reference)	Outcome	Exposure PM$_{2.5}$ Mean: (Range) in µg/m^3	Statistical Analysis Summary
			C-R relationship continued down to low-exposure levels and persisted when the data set was restricted <12 µg/m^3. The relationship was generally linear at concentrations below 14 µg/m^3.
Loop et al. (2018) Figure 3-11 U.S. Nationwide REGARDS	Nonfatal MI incidence	Median (IQR): 13.6 (2.7)	Predicted log hazard modeled as a linear function (nonlinear relationship tested using restricted cubic splines). Sensitivity analyses to test for interactions of PM$_{2.5}$ with gender, race, and urbanicity were conducted to elucidate discrepant findings (i.e., inverse relationship). No statistically significant interactions observed (p = 0.05 level). Inverse relationship between annual average PM$_{2.5}$ exposure and nonfatal MI.
Shin et al. (2019) ONPHEC Ontario, Canada	Atrial Fibrillation	Mean (IQR): 9.8 (4.0)	Identified the shape of the C-R function for fully adjusted Cox models using SCHIF (Nasari et al., 2016). Sublinear relationship observed with some evidence of potential threshold at PM$_{2.5}$ concentrations < 6 µg/m^3.
Shin et al. (2019) ONPHEC Ontario, Canada	Stroke	Mean (IQR): 9.8 (4.0)	Identified the shape of the C-R function for fully adjusted Cox models using SCHIF (Nasari et al., 2016). Linear association was observed with no evidence of a threshold.
Danesh Yazdi et al. (2019) Medicare Southeastern, U.S.	First hospital admission for stroke	NR	Penalized spline to estimate the shape of the C-R relationship, with degrees of freedom chosen based on corrected AIC values. C-R relationship continued down to low-exposure levels and persisted when the data set was restricted <12 µg/m^3. The relationship was generally linear at concentrations below 14 µg/m^3.

Table 3-3 (Continued): Summary of studies examining the concentration-response (C-R) relationship or conducted threshold analyses for long-term exposure to PM$_{2.5}$ and cardiovascular morbidity.

| Study Location—Cohort (Table/Figure from Reference)	Outcome	Exposure PM$_{2.5}$ Mean: (Range) in µg/m^3	Statistical Analysis Summary
Bai et al. (2019) Ontario, Canada ONPHEC	CHF	Mean (IQR):9.6 (3.5)	Identified the shape of the C-R function for fully adjusted Cox models using SCHIF (Nasari et al., 2016). A supralinear concentration-response relationship between CHF and PM$_{2.5}$ concentration was observed.

AIC = Akaike information criterion; C-R = concentration-response; CAC = coronary artery calcification; CHF = congestive heart failure; df = degrees of freedom; ESCAPE = European Study of Cohorts for Air Pollution Effects, HR = hazard ratio, IHD = ischemic heart disease, IQR = interquartile range; MI = myocardial infarction; REGARDS = REasons for Geographic and Racial Differences in Stroke; SCHIF = Shape Constrained Health Impact Function.

Note: **SCHIF models various shapes including supra-linear, near-linear, and sublinear forms and permits different shapes of the pollutant−outcome association in a monotonically nondecreasing manner but limits the amount of curvature in the shape.

†Studies included in the 2019 Integrated Science Assessment for Particulate Matter.

*Recent studies published since the literature cutoff date (~January 2018) for the 2019 Integrated Science Assessment for Particulate Matter.

Several studies evaluated the shape of the C-R function for the relationship between long-term PM$_{2.5}$ exposure and MI, including two analyses of the ONPHEC study (Figure 3-8 and Figure 3-9), an analysis of the U.S. Medicare population (Figure 3-10), and an analysis of the REGARDS cohort (Figure 3-11). Approximately linear relationships were observed in the ONPHEC analyses (Chen et al., 2020; Bai et al., 2019) using Shape Constrained Health Impact Function (SCHIF) method (Nasari et al., 2016), which is described as a new class of variable coefficient risk functions that can capture potentially nonlinear associations, and in the Medicare analysis using penalized splines, which is described in Section 3.1.2.1 (Danesh Yazdi et al., 2019). Both methods allow for deviations from linearity. By contrast, Loop et al. (2018) found an inverse relationship between annual average PM$_{2.5}$ exposure and nonfatal MI.
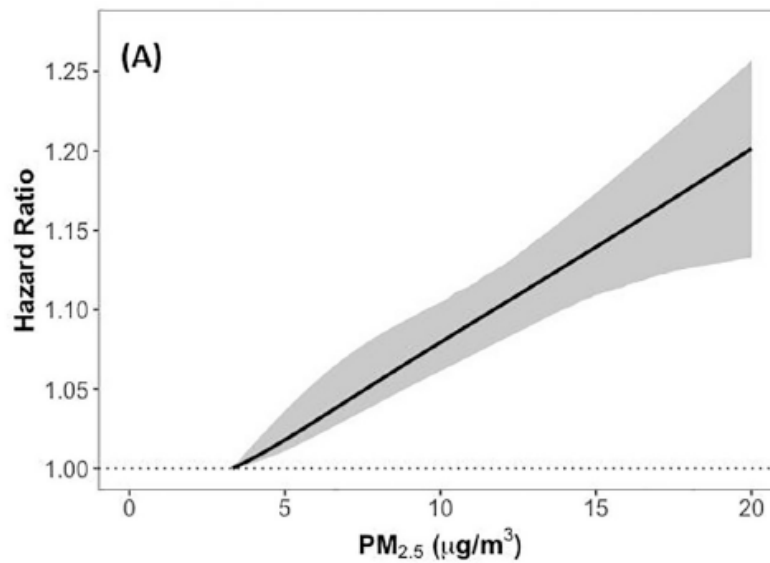
Source: Bai et al. (2019)

Note: The gray shaded area represents the 95% confidence interval.

Figure 3-8   Concentration-response relationship for the association of PM2.5 concentration with acute myocardial infarction.
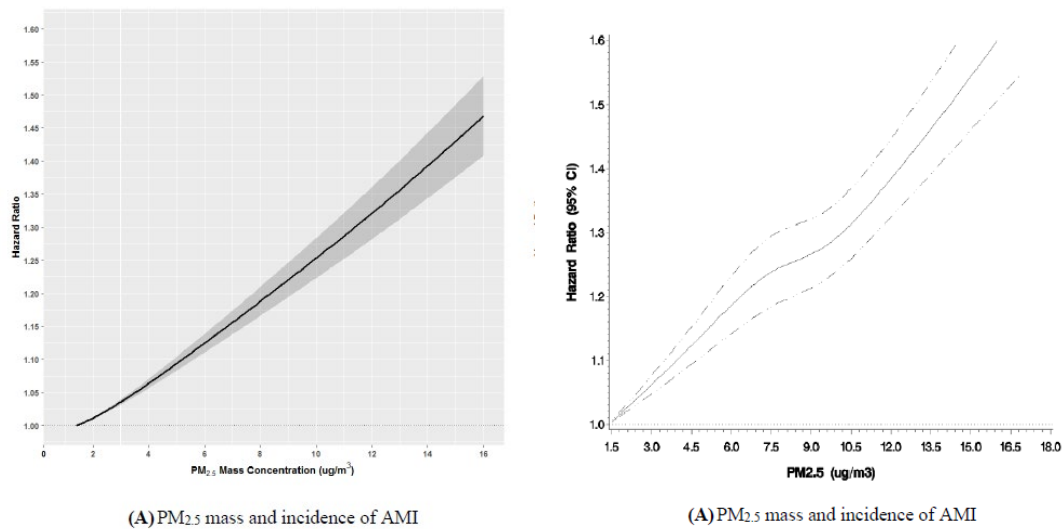
Source: Chen et al. (2020)

Note: The gray shaded area represents the 95% confidence interval.

Figure 3-9   Concentration-response relationship for the association of PM2.5 concentration with acute myocardial infarction using SCHIF (A) and penalized splines (B) with 4 degrees of freedom.

PM2.5 vs. First Admission for MI
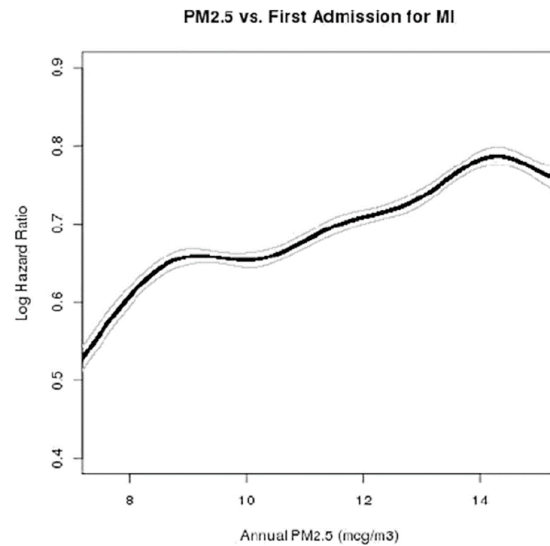
Source: Danesh Yazdi et al. (2019)

Note: The gray shaded area represents the 95% confidence interval.

Figure 3-10   Concentration-response relationship for the association of PM2.5 concentration with first admissions for myocardial infarction.
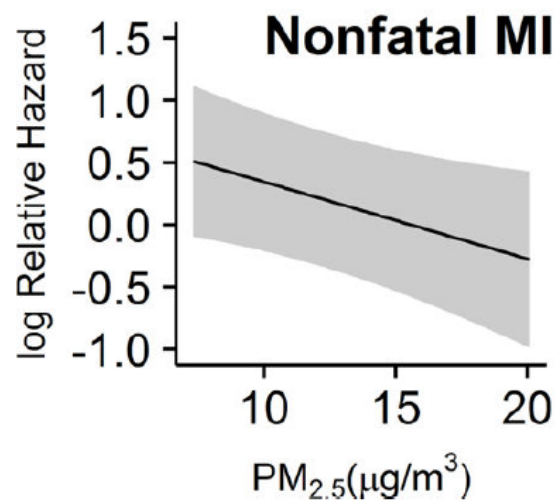
Nonfatal MI

Source: Loop et al. (2018)

Note: Gray bands are 95% prediction intervals.

Figure 3-11   Predicted log hazard for incident nonfatal myocardial infarction versus previous 1-year mean ambient PM2.5 concentration.

Several additional analyses evaluated the shape of the C-R relationship for atrial fibrillation and stroke. In analyses of ONPHEC using SCHIF, a sublinear relationship was observed for atrial fibrillation with some evidence of potential threshold at $PM_{2.5}$ concentrations < 6 μg/m^3 (Shin et al., 2019), and a linear relationship with no evidence of a threshold was observed for stroke. Danesh Yazdi et al. (2019) also found a C-R relationship that was generally linear (i.e., at $PM_{2.5}$ concentrations < 14 μg/m^3) among Medicare recipients. One study assessed the shape of the C-R function for CHF, which was observed to be supralinear, flattening at higher concentrations at approximately 14 μg/m^3 (Bai et al., 2019).

3.1.2.3.   Recent Epidemiologic Studies Examining the PM$_{2.5}$-Cardiovascular Effects Relationship through Accountability Analyses and Alternative Methods for Confounder Control

Several studies in the 2019 PM ISA were assessed and in general, supported an association between long-term $PM_{2.5}$ exposure and a variety of cardiovascular hospital admissions (2019 PM ISA, Section 6.2). However, the assessment of this outcome did not include any epidemiologic studies that conducted accountability analyses or employed alternative methods for confounder control because no such studies were prior to the literature cutoff date for the 2019 PM ISA. Since the literature cutoff date of the 2019 PM ISA, a few recent studies conducted accountability analyses or employed alternative methods for confounder control to evaluate the relationship of long-term $PM_{2.5}$ exposure and cardiovascular hospital admissions (Table A-4).

Henneman et al. (2019) utilized a difference-in-difference (DID) approach to conduct an accountability analysis of emissions reductions from coal-fueled power plants in the U.S. between 2005 and 2012 on cardiovascular hospital admission rates for acute myocardial infarction, cardiovascular stroke, heart failure, heart rhythm disorders, ischemic heart disease, peripheral vascular disease, and all cardiovascular diseases among Medicare beneficiaries. DID methods are used to estimate the effect of a specific treatment or intervention, such as reductions in coal-fueled power plant emissions, by comparing the changes in outcomes over time prior to the treatment/intervention and after. For each 1 μg/m^3 decrease in $PM_{2.5}$ concentrations, the authors reported the change in hospital admissions per 10,000 person-years and found overall reductions for all cardiovascular diseases of −8.4 (95% CI: −12.67, −4.14), −0.01 (95% CI: −0.93, 0.91) for acute myocardial infarction, −1.95 (95% CI: −3.20, −0.70) for stroke, −4.26 (95% CI: −6.09, −2.43) for heart failure, and −3.87 (95% CI: −5.67, −2.08) for ischemic heart disease. However, an increase was reported for heart rhythm disorders 0.96 (95% CI: −0.21, 2.12). Overall, Henneman et al. (2019) found that reductions in annual $PM_{2.5}$ concentrations from coal-fueled power plants resulted in corresponding reductions in a number of cardiovascular-related hospital admissions.

To examine the relationship between annual average $PM_{2.5}$ concentrations and cardiovascular-related hospital admissions including myocardial infarction, stroke, and atrial fibrillation and flutter among Medicare beneficiaries, Danesh Yazdi et al. (2021) used a doubly robust additive model

(DRAM). The steps for the approach used by Danesh Yazdi et al. (2021) is depicted in Figure 3-12. $PM_{2.5}$ concentrations were derived from a spatiotemporal ensemble model. To control for potential confounding from individual, socioeconomic, access to care variables, and copollutants (ozone and NO_2), an inverse probability weighting approach was applied through linear propensity score models to generate weights. The weights were then stabilized by taking the probability of the exposure as the numerator and the denominator as the probability density of the exposure as defined on the basis of the linear regression with $PM_{2.5}$ as the outcome and covariates and other pollutants (ozone and NO_2) as the predictors. If the inverse probability weights for the exposure and the adjustment for the weights in the outcome regression are correctly specified, it can be assumed that the estimated coefficient is unbiased. A weighted linear probability model showed that long-term exposure to $PM_{2.5}$ was associated with increased admissions across all cardiovascular hospitalization outcomes. For each 1 $\mu g/m^3$ increase in annual average $PM_{2.5}$ concentrations, the authors estimated 2,536 (95% CI: 2,383, 2,691) additional admissions for ischemic stroke, 637 (95% CI: 483, 814) additional admissions for myocardial infarction, and 1,575 (95% CI: 1,426, 1,691) additional admissions for atrial fibrillation and flutter.
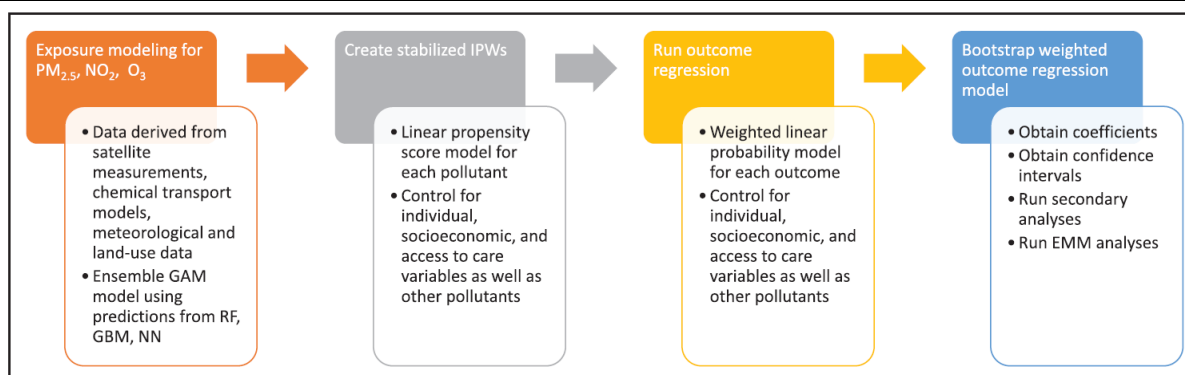
Source: Danesh Yazdi et al. (2021)

Figure 3-12   Analysis steps used by Danesh Yazdi et al. (2021) to examine long-term PM$_{2.5}$ exposure and cardiovascular-related hospital admissions.

Zigler et al. (2018) used a hybrid approach of integrating an accountability analysis with an alternative method for confounder control to examine whether attainment status for the 1997 NAAQS led to an improvement in $PM_{2.5}$ concentrations and subsequently health. By focusing on nonattainment designations, the authors are able to examine the role of local control strategies in reducing $PM_{2.5}$ concentrations that occurred above and beyond reductions due to regional strategies. Within this study, Zigler et al. (2018) employed propensity scores, within a spatial hierarchical regression model to examine whether designation of nonattainment in 2005 for the 1997 PM NAAQS, for either the annual standard of 15 $\mu g/m^3$ or the daily standard of 65 $\mu g/m^3$, led to a corresponding reduction in ambient $PM_{2.5}$

concentrations and hospitalization admission rates for cardiovascular-related outcomes (i.e., cardiovascular stroke, heart failure, heart rhythm disorders, ischemic heart disease, and peripheral vascular disease) among Medicare beneficiaries in the eastern U.S. from 2009 to 2012. Using publicly available date sources for the analysis, Zigler et al. (2018) compared average annual $PM_{2.5}$ concentrations and selected cardiovascular hospital admission rates in nonattainment areas against those in attainment areas using a two-step approach and adjusting for confounding factors that differed between the areas.

In the first step, propensity scores were used to adjust for confounders by grouping attainment and nonattainment areas based on similarities in baseline characteristics, which are detailed in Appendix A (Table A-4). Under the assumption that these baseline factors comprise all factors that differ between locations in attainment and nonattainment areas and that the factors are correlated with both the exposure (ambient $PM_{2.5}$ concentration) and each outcome (cardiovascular-related hospital admission rates), there should be no unmeasured confounders. To ensure that nonattainment areas are compared only with attainment areas with similar baseline factors, (1) propensity scores were estimated based on the probability that a monitoring location is in a nonattainment area, conditional on the baseline factors; (2) areas with features that are not comparable to other areas in the comparison group were identified and omitted (propensity score pruning); and (3) the remaining locations were grouped into quartiles, where attainment and nonattainment areas have similar baseline factors (e.g., population, $PM_{2.5}$ concentrations, demographics) within each subgroup.

In the second step, a spatial hierarchical regression model was used to predict the potential annual ambient $PM_{2.5}$ concentration in 2010–2012 that would have occurred in nonattainment areas if the designations had never occurred. For this part of the analysis, the spatial hierarchical model is estimated jointly with a log-linear model using the same confounding adjustment for propensity score group and additional covariates for each type of cardiovascular hospital admission. In addition to estimating the effect estimates for the overall average effects, a principal stratification approach was used to estimate "associative effects" and "dissociative effects." Within this study, Zigler et al. (2018) define effect estimates for the "associative effects" as the effects of the nonattainment designations on cardiovascular-related hospital admissions among areas where the nonattainment designations are estimated to reduce ambient $PM_{2.5}$ concentrations by at least 1 μg/m^3, and "dissociative effects" as the effects of the nonattainment designations estimated to not affect $PM_{2.5}$ concentrations by more than ±1 μg/m^3.

Zigler et al. (2018) reported a slight reduction in the overall average effect for hospital admission rates for cardiovascular stroke, heart failure, and ischemic heart disease and an increase in the overall effect for hospital admission rates for peripheral vascular disease; however, 95% CIs were wide and included zero. There was no evidence of a reduction in hospital admission rates for heart rhythm disorders or peripheral vascular disease. When examining the average "associative effects," the authors reported an average reduction of −2.38 (95% CI: −4.35, -0.44) and −2.60 (95% CI: −4.24, −1.14) for only heart failure and ischemic heart disease hospital admissions per 1,000 person-years, respectively. The authors reported a similar pattern of associations for the average "dissociative effects," that is, slight reductions in

hospital admission rates for only cardiovascular stroke and heart failure with wide 95% CIs that included the null. Overall, the results of Zigler et al. (2018) provide evidence that reductions in ambient $PM_{2.5}$ concentrations and the selected cardiovascular hospital admissions could not be conclusively attributed to nonattainment designations against the backdrop of other regional strategies that impacted the eastern U.S.

The addition of these recent studies further supports the findings from the studies of the 2019 PM ISA. Overall, these studies reported consistent findings that long-term $PM_{2.5}$ exposure is associated with increased hospital admissions for a variety of cardiovascular disease outcomes among large nationally representative study populations. The addition of studies that use methods to reduce uncertainties related to potential confounding bias with statistical methods and/or study design approaches, like DRAM used by Danesh Yazdi et al. (2021) or the DID approach used by Henneman et al. (2019), further increase confidence in the relationship between long-term $PM_{2.5}$ exposure and cardiovascular effects.

3.1.2.4.   Summary of Recent Evidence in the Context of the 2019 Integrated Science Assessment for Particulate Matter Causality Determination for Long-Term PM$_{2.5}$ Exposure and Cardiovascular Effects

Recent epidemiologic studies published since the 2019 PM ISA support and extend the evidence that contributed to the conclusion of a *causal relationship* between long-term $PM_{2.5}$ exposure and cardiovascular effects. Numerous U.S. and Canadian cohort studies conducted in locations where the long-term $PM_{2.5}$ concentration are less than 13 $\mu g/m^3$ add to the strong evidence base that was characterized in the 2019 PM ISA describing the relationship between long-term $PM_{2.5}$ and cardiovascular mortality, and specifically IHD- and stroke-related mortality. Overall, these recent cardiovascular mortality studies reported positive associations at varying spatial scales and across different exposure assessment and statistical methods. The associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality generally persisted in models that were adjusted for ozone, NO_2, $PM_{10-2.5}$, or SO_2, and most analyses of the C-R function supported a linear, no-threshold relationship for cardiovascular mortality, especially at lower ambient concentrations of $PM_{2.5}$ (Section 3.2.2.2.2).

Although results were not entirely consistent, evidence of positive associations between long-term $PM_{2.5}$ exposure and cardiovascular morbidity (i.e., CHD, stroke, and atherosclerosis progression) were observed in epidemiologic studies reviewed in the 2019 PM ISA, providing coherence with the mortality findings described above. Recent studies support and the extend findings characterized in the 2019 PM ISA, providing additional evidence of positive associations between long-term $PM_{2.5}$ exposure and cardiovascular outcomes including MI, stroke, arrhythmias, atherosclerosis, HF, and hypertension. Although positive associations are not reported in all studies, these recent studies also support and extend the most consistent evidence of cardiovascular effects reviewed in the 2019 PM ISA, which described positive associations among those with preexisting diseases and among patients that are followed after a cardiac event or procedure (Rhinehart et al., 2020; Ward-Caviness et al., 2020; Malik et

al., 2019; Weaver et al., 2019). Recent studies also support and extend the evidence in the 2019 PM ISA regarding effect measure modification by income and SES (Section 3.3.3). Together these recent studies examining effect measure modification may explain inconsistency observed across cardiovascular morbidity studies by identifying factors that determine the heterogeneity.

The limited number of studies reviewed in the 2019 PM ISA found that risk estimates remained largely unchanged after adjustment for $PM_{10-2.5}$, NO_2, and $PM_{2.5}$ from traffic sources. The few recent analyses report some attenuation of risk estimates in models adjusted for O_3 and NO_2. Recent studies also support and extend the evidence in the 2019 PM ISA pertaining to the joint effects of multiple pollutants indicating that associations may be modified by oxidant gases, $PM_{2.5}$ composition and long-term exposure to NO_2. Further, recent studies support and extend the evidence in the 2019 PM ISA pertaining to the shape of the C-R function for cardiovascular morbidity effects. Although still limited in number, recent studies characterizing the C-R relationship provide a more thorough examination of potential for departures from linearity. Evidence from these studies is generally consistent with that presented in the 2019 PM ISA, and shows a linear, no-threshold C-R relationship for most CVD outcomes. However, there is some evidence for a sublinear or supralinear C-R relationship for specific outcome (i.e., CHF and AF). Finally, a few recent epidemiologic studies that employed alternative methods for confounder control to reduce uncertainties related to potential confounding bias provide additional support for a relationship between long-term $PM_{2.5}$ exposure and cardiovascular effects.

3.2. Mortality

3.2.1.   Short-Term PM$_{2.5}$ Exposure

The following sections represent a summary of the evidence and the corresponding causality determination for short-term $PM_{2.5}$ exposure and mortality presented within the 2019 PM ISA (Section 3.2.1.1) along with an evaluation of recent epidemiologic studies that fall within the scope of the Supplement (i.e., studies conducted in the U.S. and Canada) and were published since the literature cutoff date of the 2019 PM ISA (Section 3.2.1.2). [16] In addition, with the expansion of epidemiologic studies that used statistical approaches that attempt to more extensively account for confounders and are more robust to model misspecification (i.e., used alternative methods for confounder control), recent studies that employed such methods are also evaluated (Section 3.2.1.3), which can further inform the relationship between short-term $PM_{2.5}$ exposure and mortality. Finally, a summary of the results of recent studies evaluated within the section is presented in the context of the scientific conclusions detailed in the 2019 PM ISA (Section 3.2.1.4). The evaluation of recent studies on short-term $PM_{2.5}$ exposure and mortality

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[16] Throughout this section, as detailed in the Preface of the 2019 PM ISA (Section P.3.2.2), risk estimates from epidemiologic studies examining short-term exposures are for a 10 μg/m^3 increase in 24-hour avg $PM_{2.5}$ concentrations, unless otherwise noted.

presented in this Supplement adds to the collective body of evidence reviewed in the process of reconsidering the PM NAAQS.

3.2.1.1.   Summary and Causality Determination from 2019 Integrated Science Assessment for Particulate Matter

Multicity studies evaluated since the completion of the 2009 PM ISA continue to provide evidence of primarily positive associations between short-term $PM_{2.5}$ exposures and total (nonaccidental) mortality from studies conducted mostly in urban areas using traditional exposure assignment approaches (i.e., average of all available monitors) as well as studies with a larger spatial coverage (i.e., urban and rural areas) employing new methods using multiple types of $PM_{2.5}$ data (i.e., combination of monitoring, satellite, and land use regression [LUR]). Additionally, the evidence from studies evaluated in the 2019 PM ISA further substantiated the relationship between short-term $PM_{2.5}$ exposure and mortality by providing additional information on potential copollutant confounding; effect modification (e.g., stressors, pollutants, season); geographic heterogeneity in associations; and the shape of the C-R relationship, which collectively reaffirmed that a *causal relationship* exists between short-term $PM_{2.5}$ exposure and mortality. The body of evidence for total mortality was supported by generally consistent positive associations with cardiovascular and respiratory mortality.

In addition to evaluating epidemiologic studies that examined the relationship between short-term $PM_{2.5}$ exposure and mortality, the 2019 PM ISA characterized whether evidence supported biologically plausible mechanisms by which short-term $PM_{2.5}$ exposure could lead to mortality (2019 PM ISA, Section 11.1.1). This evaluation consisted of an assessment of animal toxicological, controlled human exposure, and epidemiologic studies of morbidity effects that are the largest contributors to total (nonaccidental) mortality, specifically, cardiovascular and respiratory morbidity (2019 PM ISA, Section 6.1.1 and Section 5.1.1, respectively). Plausible mechanisms were identified by which inhalation exposure to $PM_{2.5}$ could progress from initial events to endpoints relevant to the cardiovascular system and to population outcomes such as ED visits and hospital admissions due to cardiovascular disease, particularly ischemic heart disease and congestive heart failure (2019 PM ISA, Section 6.1.1). Similarly, available evidence was characterized by which inhalation exposure to $PM_{2.5}$ could progress from initial events to endpoints relevant to the respiratory system (2019 PM ISA, Section 5.1.1). However, the evidence for how the initial events and subsequent endpoints could lead to the observed increases in respiratory ED visits and hospital admissions, in particular for chronic obstructive pulmonary disease (COPD) and asthma was limited. In summary, although there was coherence of effects across the scientific disciplines (i.e., animal toxicological, controlled human exposure studies, and epidemiologic) and biological plausibility for $PM_{2.5}$-related cardiovascular (2019 PM ISA, Chapter 6) and respiratory (2019 PM ISA, Chapter 5) morbidity, there was strong evidence indicating biological plausibility for $PM_{2.5}$-related cardiovascular mortality with more limited evidence for respiratory mortality.

This section describes the evaluation of evidence for total (nonaccidental) mortality conducted in the 2019 PM ISA, with respect to the causality determination for short-term exposures to PM$_{2.5}$ using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015). The key evidence, as it relates to the causal framework, is summarized in Table 3-4.

Table 3-4   Summary of evidence for a *causal relationship* between short-term PM$_{2.5}$ exposure and total mortality from the 2019 Integrated Science Assessment for Particulate Matter.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References and Sections in the 2019 PM ISA[b]	PM$_{2.5}$ Concentrations Associated with Effects ($\mu g/m^3$)[c]
Consistent epidemiologic evidence from multiple studies at relevant PM$_{2.5}$ concentrations	Increases in mortality in multicity studies conducted in the U.S., Canada, Europe, and Asia. Total mortality associations, further supported by increases in cardiovascular and respiratory mortality in multicity studies conducted in the U.S., Canada, Europe, and Asia.	Section 11.1.2 Figure 11-1 Figure 11-2 Section 5.1.9 Section 6.1.9	Mean 24-h avg: U.S. and Canada: 4.37−17.97 Europe: 13−27.7d Asia: 11.8−69.9 Table 11-1
Epidemiologic evidence from copollutant models provides some support for an independent PM$_{2.5}$ association	The magnitude of PM$_{2.5}$ associations remain positive, but in some cases are reduced with larger confidence intervals in copollutant models with gaseous pollutants and PM$_{10-2.5}$, supporting the limited evidence from the 2009 PM ISA. Further support comes from copollutant analyses indicating positive associations for cardiovascular and respiratory mortality. Recent studies that examined potential copollutant confounding are limited to studies conducted in Europe and Asia. When reported, correlations with gaseous copollutants were primarily in the low ($r < 0.4$) to moderate ($r \geq 0.4$ or < 0.8) range.	Section 11.1.4 Figure 11-3 Section 5.1.10.1 Section 6.1.14.1	
Epidemiologic evidence supports a linear, no-threshold C-R relationship	Recent multicity studies conducted in the U.S. and Europe provide direct evidence of a linear, no-threshold C-R relationship at lower PM$_{2.5}$ concentrations with initial evidence of a steeper slope, but extensive systematic evaluations of alternatives to linearity have not been conducted.	Section 11.1.10 Shi et al. (2015) Lee et al. (2015) Di et al. (2017a)	

Table 3-4 (Continued): Summary of evidence for a *causal relationship* between short-term PM$_{2.5}$ exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References and Sections in the 2019 PM ISA[b]	PM$_{2.5}$ Concentrations Associated with Effects (µg/m³)[c]
Biological plausibility from cardiovascular morbidity evidence	Strong evidence for coherence of effects across scientific disciplines and biological plausibility for a range of cardiovascular effects in response to short-term PM$_{2.5}$ exposure, specifically for ischemic events and heart failure, which is supported by experimental evidence and epidemiologic studies examining hospital admissions and ED visits. The collective body of cardiovascular morbidity evidence provides biological plausibility for a relationship between short-term PM$_{2.5}$ exposure and cardiovascular mortality, which comprises ~33% of total mortality.	Section 6.1.16 Table 6-33	
Limited biological plausibility from respiratory morbidity evidence	Limited evidence for coherence of effects across scientific disciplines and biological plausibility, with the strongest evidence for exacerbations of COPD and asthma. The collective body of respiratory morbidity evidence provides limited biological plausibility for a relationship between short-term PM$_{2.5}$ exposure and respiratory mortality, which comprises ~9% of total mortality.	Section 5.1.12 Table 5-18	
Uncertainty regarding geographic heterogeneity in PM$_{2.5}$ associations	Multicity U.S. studies demonstrate city-to-city and regional heterogeneity in PM$_{2.5}$-mortality associations. Evidence supports that a combination of factors, including composition and exposure factors may contribute to the observed heterogeneity.	Section 11.1.6.3	

Note: This table corresponds to Table 11-4 in the 2019 PM ISA.

avg = average; COPD = chronic obstructive pulmonary disease; C-R = concentration-response; ED = emergency department; h = hour; PM = particulate matter; PM$_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 µm; PM$_{10-2.5}$ = particulate matter with a nominal mean aerodynamic diameter greater than 2.5 µm and less than or equal to 10 µm; *r* = correlation coefficient.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs U.S. EPA (2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to the causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described in the 2019 PM ISA.

[c]Describes the PM$_{2.5}$ concentrations with which the evidence is substantiated.

[d]Median concentration from Samoli et al. (2013).

[e]Statistics taken from NHLBI (2017).

Collectively, the evidence from multicity studies of short-term $PM_{2.5}$ exposures and mortality evaluated in the 2019 PM ISA generally demonstrated positive associations with total (nonaccidental) mortality, with increases ranging from 0.19% (Lippmann et al., 2013b) to 2.80% (Kloog et al., 2013) at lags of 0 to 1 days in single-pollutant models. These results were further supported by initial studies employing causal inference and quasi-experimental statistical approaches (2019 PM ISA, Section 11.1.2.1). Whereas most studies relied on assigning exposure using data from ambient monitors, some of the studies evaluated also employed hybrid modeling methods, which use additional sources of $PM_{2.5}$ data (i.e., monitor, satellite, and LUR) to estimate $PM_{2.5}$ concentrations and assign exposure, allowing for the inclusion of less urban and rural locations in analyses (Lee et al., 2015; Shi et al., 2015; Kloog et al., 2013). The studies evaluated expanded the assessment of potential copollutant confounding on the $PM_{2.5}$-mortality relationship, and provided additional evidence supporting the conclusion that $PM_{2.5}$ associations remain positive and relatively unchanged in copollutant models with both gaseous pollutants and $PM_{10-2.5}$, but this conclusion was based on a limited number of multicity studies conducted in Europe and Asia where mean 24-hour avg $PM_{2.5}$ concentrations are higher (2019 PM ISA, Table 3-1). However, the low ($r < 0.4$) to moderate correlations ($r = 0.4 < 0.7$) between $PM_{2.5}$ and gaseous pollutants and $PM_{10-2.5}$ increased the confidence in $PM_{2.5}$ having an independent effect on mortality.

The positive associations for total (nonaccidental) mortality reported across the majority of studies evaluated was further supported by analyses focusing on cause-specific mortality that continue to provide evidence of generally consistent positive associations with both cardiovascular and respiratory mortality, except in the case of a multicity study conducted in Europe (Lanzinger et al., 2016). Risk estimates for cardiovascular mortality ranged from 0.09% (Lippmann et al., 2013b) to 2.32% (Lee et al., 2015), while those for respiratory mortality ranged from 0.09% (Lee et al., 2015) to 2.30% (Janssen et al., 2013), but overall associations tended to be larger in magnitude for respiratory mortality. For both cardiovascular and respiratory mortality there was a limited assessment of potential copollutant confounding, but for both outcomes, initial evidence indicated that associations remained positive and relatively unchanged in models with gaseous pollutants and $PM_{10-2.5}$, which further supported the copollutant analyses conducted for total (nonaccidental) mortality. The strong evidence for ischemic events and heart failure detailed in the assessment of cardiovascular morbidity (2019 PM ISA, Chapter 6), provided strong biological plausibility for $PM_{2.5}$-related cardiovascular mortality, which comprises the largest percent of total mortality [i.e., ~33%; NHLBI (2017)]. Although there was evidence for exacerbations of COPD and asthma, the collective body of respiratory morbidity evidence provided limited biological plausibility for $PM_{2.5}$-related respiratory mortality (2019 PM ISA, Chapter 5).

In addition to examining potential copollutant confounding, a number of studies evaluated in the 2019 PM ISA also assessed whether statistical models adequately accounted for temporal trends and weather covariates. Across studies that evaluated model specification, $PM_{2.5}$-mortality, associations remained positive, although in some cases were attenuated, when using different approaches to account for temporal trends or weather covariates (2019 PM ISA, Section 11.1.5). Seasonal analyses continued to

provide evidence that associations were larger in magnitude during warmer months, but it remained unclear whether copollutants confound the associations observed. In addition to seasonal analyses, some studies also examined whether temperature modified the $PM_{2.5}$-mortality relationship. Initial evidence indicated that the $PM_{2.5}$-mortality association may be larger in magnitude at lower and higher temperatures, but this observation has not been substantiated by studies conducted in the U.S. (2019 PM ISA, Section 11.1.6.2).

At the completion of the 2009 PM ISA, one of the main uncertainties identified was the regional and city-to-city heterogeneity in $PM_{2.5}$-mortality associations observed in multicity studies. Studies evaluated in the 2019 PM ISA examined both city specific as well as regional characteristics to identify the underlying factors that contribute to this heterogeneity (2019 PM ISA, Section 11.1.6.3). Analyses focusing on effect modification of the $PM_{2.5}$-mortality relationship by $PM_{2.5}$ components, regional patterns in $PM_{2.5}$ components, and city-specific differences in composition and sources indicated some differences in the $PM_{2.5}$ composition and sources across cities and regions, but these differences did not fully explain the heterogeneity observed. Additional studies examined whether exposure factors play a role in explaining the heterogeneity in $PM_{2.5}$-mortality associations and found that some factors related to housing stock and commuting, as well as city-specific factors (e.g., land use, port volume, and traffic information), also explain some of the observed heterogeneity. Collectively, the studies evaluated indicated that the heterogeneity in $PM_{2.5}$-mortality risk estimates cannot be attributed to one factor, but instead to a combination of factors, including, but not limited to, compositional and source differences, as well as exposure differences.

A number of studies evaluated conducted systematic evaluations of the lag structure of associations for the $PM_{2.5}$-mortality relationship by examining either multiday lags or a series of single-day lags, and these studies continued to support an immediate effect (i.e., lag 0 to 1 days) of short-term $PM_{2.5}$ exposures on mortality (2019 PM ISA, Section 11.1.8.1). Studies also conducted analyses comparing the traditional 24-hour avg exposure metric with a subdaily metric (i.e., 1-hour max). These initial studies provided evidence of a similar pattern of associations for both the 24-hour avg and 1-hour max metric, with a larger association for the 24-hour avg metric. Additionally, some studies examined alternative exposure metrics representing size fractions smaller than $PM_{2.5}$ and reflecting number concentration (NC) and surface-area concentration (SC). The generally positive associations reported with mortality for these smaller PM size fractions supported the larger body of $PM_{2.5}$-mortality evidence, but it is difficult to compare NC and SC metrics with the traditional mass-based metric.

Building off the initial analysis of the C-R relationship between short-term PM exposure and mortality that focused on PM_{10}, multicity studies conducted in the U.S. and Europe examined the shape of the C-R relationship and whether a threshold exists specifically for $PM_{2.5}$ (2019 PM ISA, Section 11.1.10). These studies used different statistical approaches and consistently demonstrated a linear relationship with no evidence of a threshold. Additionally, recent analyses conducted at lower $PM_{2.5}$ concentrations (i.e., 24-hour avg $PM_{2.5}$ concentrations $< 30 \ \mu g/m^3$) provided initial evidence

indicating that PM$_{2.5}$-mortality associations persist and may be stronger (i.e., a steeper slope) at lower concentrations. However, to date, extensive analyses have not been conducted to systematically explore alternatives to linearity when examining the shape of the PM$_{2.5}$-mortality C-R relationship.

Overall, epidemiologic studies evaluated in the 2019 PM ISA built upon and further reaffirm the conclusions of the 2009 PM ISA for total mortality. The evidence particularly from the assessment of PM$_{2.5}$-related cardiovascular morbidity, with more limited evidence from respiratory morbidity, provided biological plausibility for mortality from short-term PM$_{2.5}$ exposures. In conclusion, the primarily positive associations observed across studies conducted in various locations was further supported by the results from copollutant analyses that indicated robust associations, along with evidence from analyses of the C-R relationship. **Collectively, this body of evidence is sufficient to conclude that a causal relationship exists between short-term PM$_{2.5}$ exposure and total mortality.**

3.2.1.2.   Recent U.S. and Canadian Epidemiologic Studies

The few recent multicity studies conducted in the U.S. and Canada build upon the strong epidemiologic evidence base evaluated in the 2019 PM ISA, as well as in previous assessments, which provided the scientific rationale supporting a *causal relationship* between short-term PM$_{2.5}$ exposure and mortality (Section 3.1.1.1). In addition to examining the relationship between short-term PM$_{2.5}$ exposure and all-cause or nonaccidental mortality (Section 3.1.1.2.1) and cause-specific mortality (Section 3.1.1.2.2), additional analyses within these recent studies also further examined issues relevant to expanding the overall understanding of the effect of short-term PM$_{2.5}$ exposure on mortality. Specifically, recent studies have assessed potential copollutant confounding (Section 3.1.1.2.3), examined effect modification of the PM$_{2.5}$-mortality relationship (Section 3.1.1.2.4), the lag structure of associations (Section 3.1.1.2.5), and assessed the shape of the concentration-response (C-R) relationship (Section 3.1.1.2.6). The following sections present an evaluation of recent multicity studies that inform each of the aforementioned topics within the context of the evidence base evaluated and summarized in the 2019 PM ISA. Study-specific details (e.g., study population, exposure assessment approach, confounders considered) for the epidemiologic studies evaluated in this section are presented in Appendix A (Table A-5).

3.2.1.2.1.   All-Cause and Total (Nonaccidental) Mortality

Since the literature cutoff date for the 2019 PM ISA, a limited number of multicity studies have been conducted within the U.S. and Canada (Shin et al., 2021a; Liu et al., 2019; Lavigne et al., 2018). Although few in number, these recent studies add to the extensive number of multicity studies evaluated in the 2019 PM ISA that were conducted globally, specifically in locations where mean 24-hour concentrations were generally < 20 µg/m^3 (2019 PM ISA, Section P.3.1). Taken together, these studies

provide consistent evidence of positive associations between short-term $PM_{2.5}$ exposure and mortality across diverse geographic locations; in populations with a wide range of demographic characteristics; and using a variety of statistical models, approaches to confounder adjustment, and exposure assessment approaches (Figure 3-13).
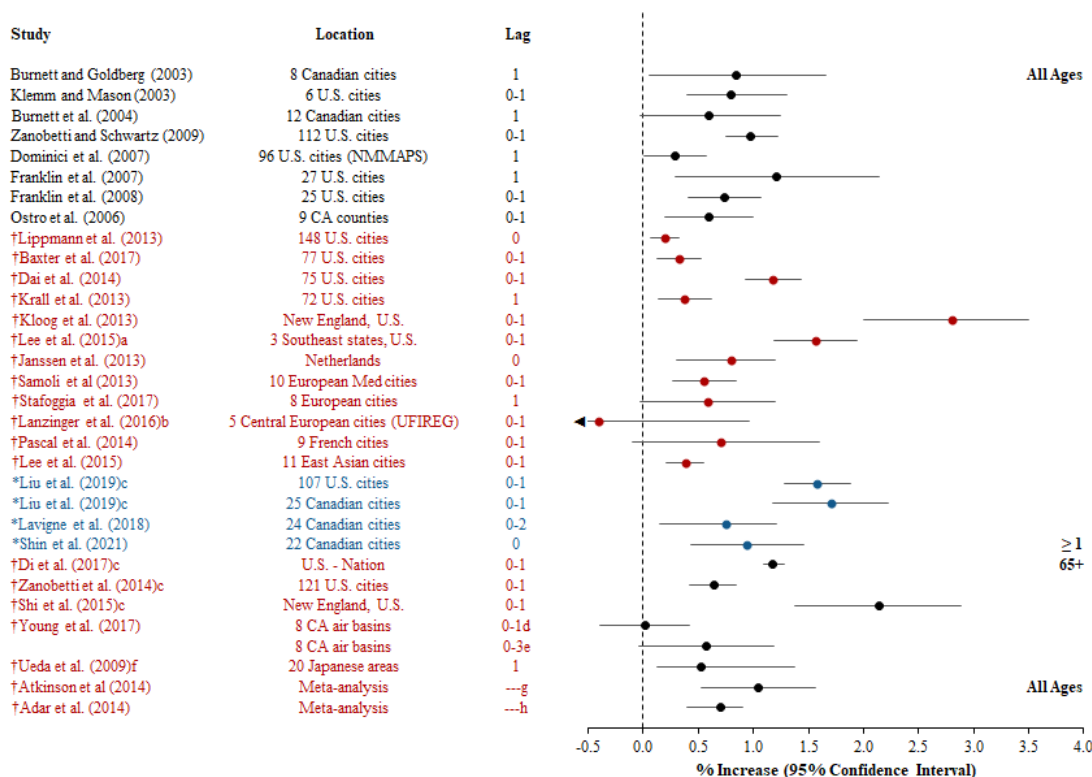
Source: Update of Figure 11-1, 2019 PM ISA.

avg = average; μg/m^3 = microgram per cubic meter; NMMAPS = National Morbidity, Mortality, and Air Pollution Study; PM = particulate matter; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm; UFIREG = Ultrafine Particles—An Evidence-Based Contribution to the Development of Regional and European Environmental and Health Policy.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) 2019 PM ISA. Black circles = U.S. and Canadian multicity studies evaluated in the 2004 PM AQCD and 2009 PM ISA. Red circles = multicity studies and meta-analyses published since the completion of the 2009 PM ISA. Blue circles = multicity U.S. and Canadian studies published since the literature cutoff date of the 2019 PM ISA. Risk estimates are standardized to a 10 μg/m^3 increase in $PM_{2.5}$ concentrations.

[a]Results are from modeled $PM_{2.5}$ analysis, analysis focusing on measured $PM_{2.5}$ reported 1.21% (95% CI: 0.94, 1.47).

[b]Only four of the five cities measured $PM_{2.5}$.

[c]Shi et al. (2015), Zanobetti et al. (2014), and Liu et al. (2019) only had data for all-cause mortality including accidental mortalities.

[d]Main model used in Young et al. (2017) included current and average of 3 previous days daily maximum temperature, daily minimum temperature, and maximum daily relative humidity.

[e]Sensitivity analysis in Young et al. (2017) focusing on only the San Francisco Bay air basin, dropping out the maximum daily relative humidity term, where the shortest duration of lag days examined was 0−3 days.

[f]Ueda et al. (2009) presented results for three different modeling approaches, which are presented here: generalized additive model (GAM), generalized linear model (GLM), and case-crossover.

[g]Atkinson et al. (2014) primarily focused on single-day lag results.

[h]Adar et al. (2014) focused on single-day lag results, specifically lag 0, 1, or 2.

Figure 3-13   Summary of associations between short-term PM_{2.5} exposure and total (nonaccidental) mortality in multicity studies.

Recent studies that conducted multicity analyses in the U.S. and Canada include a large international study that performed a global multicity analysis (Liu et al., 2019) and a few studies in Canada that relied on data from over 20 cities (Shin et al., 2021a; Lavigne et al., 2018). Using the Multi-City Multi-Country (MCC) Collaborative Research Network, Liu et al. (2019) was able to collect data globally, resulting in a data set consisting of air pollution and mortality data from 652 urban areas in 24 countries from 1986 to 2015. Although the goal of the study was to estimate a global estimate of the association between short-term $PM_{2.5}$ exposure and mortality, the authors presented country specific estimates as well, including for the U.S. and Canada. The authors applied a uniform statistical model across all of the cities within the study consisting of a quasi-Poisson general additive model that controlled for temporal trends and weather covariates. In a second-stage analysis, the authors used a random-effects model to pool city-specific estimates into a country-specific estimate. All analyses relied on $PM_{2.5}$ data for which the highest and lowest 5% of data was trimmed to remove outliers. In analyses of 25 Canadian cities from 1986 to 2011 and 107 U.S. cities from 1987 to 2006, the authors reported a 1.70% (95% CI: 1.17, 2.23) and 1.58% (95% CI: 1.28, 1.88) increase in mortality, respectively, at lag 0−1 days.

Recent studies conducted in Canada by Lavigne et al. (2018) and Shin et al. (2021a) focused on more recent years of data, 1998−2011 and 2001−2012, respectively, in comparison to Liu et al. (2019). Lavigne et al. (2018) focused on examining whether oxidant gases modified the association between short-term $PM_{2.5}$ exposure and mortality in 24 Canadian cities (discussed in more detail in Section 3.2.1.2.4). In a time-stratified case-crossover analysis that adjusted for both mean temperature and location-specific temperature distributions and relative humidity, the authors reported a 0.76% (95% CI: 0.15, 1.21) increase in mortality at lag 0−2 days. The results of Lavigne et al. (2018) are consistent with those reported by Shin et al. (2021a) in a time-series study of 22 Canadian cities. The authors examined single-day lags ranging from 0 to 2 days using a two-stage hierarchical model consisting of a Poisson model in the first stage to examine city-specific associations and a Bayesian random effects model in the second stage to combine city-specific effects into a national estimate. Shin et al. (2021a) reported associations with mortality similar in magnitude at lag 0 (0.94% [0.43, 1.46]) and 1 day (0.90% [95% CI: 0.33, 1.41]) with no evidence of an association at lag 2. Although it is unclear as to why the magnitude of associations reported in Lavigne et al. (2018) and Shin et al. (2021a) differ from those reported by Liu et al. (2019), even though both are using a similar subset of cities, it could be attributed to the more recent years of data used in Lavigne et al. (2018) and Shin et al. (2021a) where there has been a decreasing trend in $PM_{2.5}$ concentrations (Shin et al., 2021a).

Sudden Nonaccidental Mortality

The 2009 PM ISA reviewed a handful of small studies examining the association between $PM_{2.5}$ exposure and out-of-hospital cardiac arrest (OHCA). No evidence of an association was reported. Section 6.1.4.1 of the 2019 PM ISA evaluated studies published since the 2009 PM ISA, which provided evidence for an association between short-term $PM_{2.5}$ exposure and OHCA. This association was typically

observed with $PM_{2.5}$ concentrations averaged over the past 0 to 2 days, although associations with $PM_{2.5}$ concentrations as far back as 4 days before the event have been reported. Additionally, all of the studies assessed in the 2009 and 2019 ISAs relied on a single monitor or an average of fixed-site monitors to estimate $PM_{2.5}$ exposure, which restricts the study population to people living near monitors. While the previously evaluated studies focused on a cardiovascular outcome (i.e., OHCA) and as a result were discussed within the evidence for short-term $PM_{2.5}$ exposure and cardiovascular effects, the results of these previous studies are summarized here as they can inform a recent study by Rappazzo et al. (2019) that examined out-of-hospital sudden unexpected deaths.

Rappazzo et al. (2019) conducted a time-stratified case-crossover analysis to examine the relationship between short-term $PM_{2.5}$ exposure and out-of-hospital nonaccidental sudden unexpected deaths in a small population of individuals (n = 399) over a 2-year period that resided in Wake County, NC. In analyses examining both single-day lags ranging from 0 to 3 days and a 0−1 day lag, the authors reported a positive association at lag 1 (OR = 1.39 [95% CI: 0.96, 1.99]) that was smaller in magnitude when using a 0−1 day lag (OR = 1.18 [95% CI: 0.79, 1.78]). However, due to the small sample size within this study confidence intervals are large. In addition to single-pollutant models, the authors examined copollutant models across the single-day lags and reported that $PM_{2.5}$ associations are relatively unchanged in models with NO_2, SO_2, ozone, and CO. This initial study focusing out-of-hospital sudden unexpected deaths from all nonaccidental causes, provides evidence consistent with the relatively limited number of previous studies examining OHCA.

3.2.1.2.2.   Cause-specific Mortality

Single and multicity studies evaluated in the 2009 PM ISA that examined cause-specific mortality reported consistent positive associations with both cardiovascular and respiratory mortality. The magnitude of the association was larger for respiratory mortality, but these associations also had wider confidence intervals due to the smaller number of respiratory-related deaths than cardiovascular-related deaths. Studies evaluated in the 2019 PM ISA added to this body of evidence but provided more consistent evidence of associations for cardiovascular mortality compared with respiratory mortality. Recent multicity studies conducted in Canada provide additional support for an association with cardiovascular mortality (Lavigne et al., 2018). Consistent with the evidence assessed in previous ISAs, recent studies report more variable results with wider confidence intervals for respiratory mortality (Shin et al., 2021b; Lavigne et al., 2018).
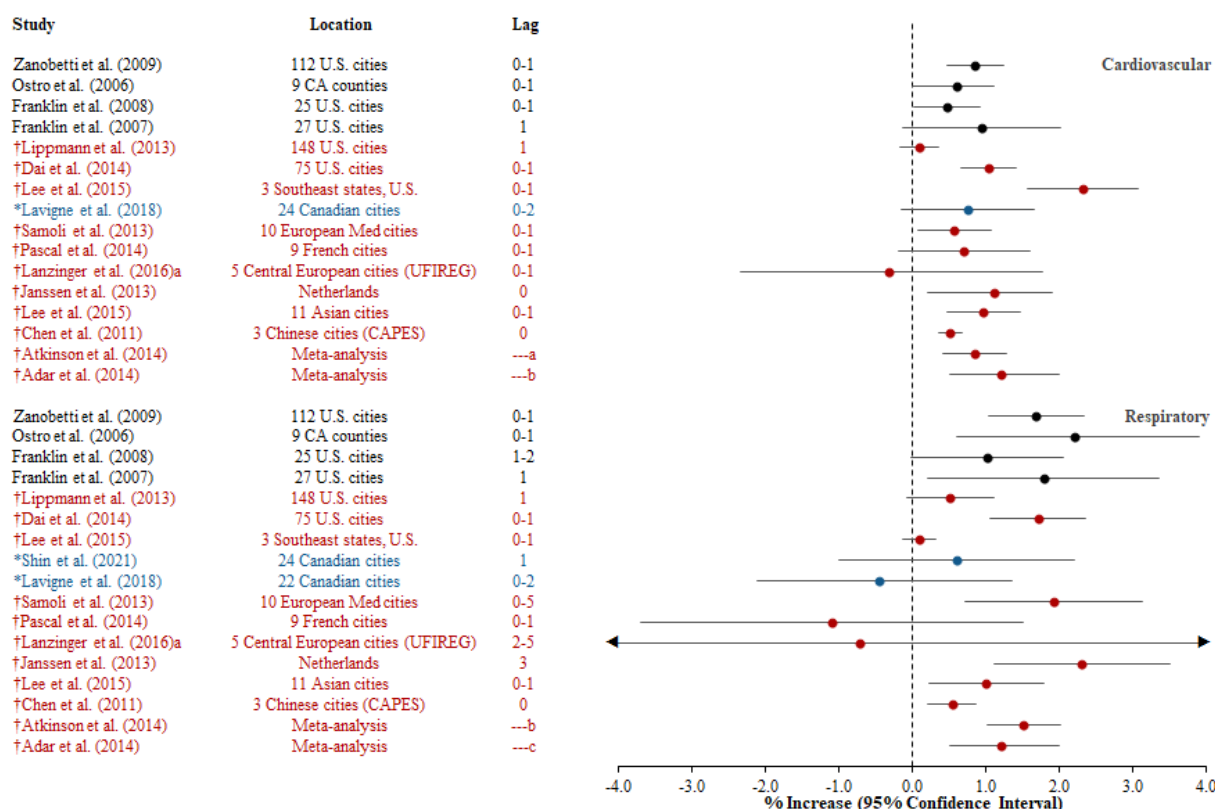
Source: Update of Figure 11-2, 2019 PM ISA.

avg = average; μg/m³ = microgram per cubic meter; PM = particulate matter; PM₂.₅ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm; UFIREG = Ultrafine Particles—An Evidence-Based Contribution to the Development of Regional and European Environmental and Health Policy.

Note: †Studies published since the 2009 PM ISA. *U.S. and Canadian studies published since the literature cutoff date (~January 2018) for the 2019 PM ISA. Studies organized by lag structure, therefore, cardiovascular and respiratory mortality results are not in the same order. Black circles = U.S. and Canadian multicity studies evaluated in the 2004 PM AQCD and 2009 PM ISA. Red circles = multicity studies and meta-analyses published since the literature cutoff date of the 2009 PM ISA. Risk estimates are standardized to a 10 μg/m³ increase in PM₂.₅ concentrations. All ages examined for all studies except Lanzinger et al. (2016) and Shin et al. (2021b) which focused on ages ≥ 1 year old.

ᵃOnly four of the five cities measured PM₂.₅.

ᵇAtkinson et al. (2014) primarily focused on single-day lag results.

ᶜAdar et al. (2014) focused on single-day lag results, specifically lag 0, 1, or 2.

Figure 3-14   Summary of associations between short-term PM₂.₅ exposure and cardiovascular and respiratory mortality in multicity studies.

3.2.1.2.3.   Potential Copollutant Confounding of the PM₂.₅-Mortality Relationship

As discussed in Section 3.1.2.2.8, one approach to assessing the independence of the association between exposure to PM₂.₅ and a health effect, such as short-term PM₂.₅ exposure and mortality, can be examined is through the use of copollutant models. Appendix (Table A-1) to the 2019 PM ISA notes that copollutant models are not without their limitations, such as instances where correlations are high between pollutants resulting in greater bias in results. However, in assessing the results from copollutant

models a change in the PM$_{2.5}$ risk estimate, after adjustment for a copollutant, may indicate the potential for confounding.

At the time of the 2009 ISA, only a few studies had assessed the potential for confounding of the PM$_{2.5}$-mortality association by co-occurring pollutants. In contrast, the 2019 ISA included a number of multicity studies that used copollutant models to evaluate this issue, including studies that examined both gaseous pollutants and other particle size fractions. These studies reported that associations were relatively unchanged in copollutant models, albeit with wider confidence intervals than single pollutant models (2019 PM ISA, Figure 11-3).

Of the recent multicity studies conducted in the U.S. and Canada, only Lavigne et al. (2018) conducted an assessment of copollutant confounding, with a focus on oxidant gases. Within this study, oxidant gases were defined as the daily combined oxidant capacity of ozone and NO$_2$ based on the redox-weighted averages of both pollutants. In a copollutant model with oxidant gases, the association between short-term PM$_{2.5}$ exposure and mortality is unchanged compared with the single pollutant model with both reporting a 0.76% increase in mortality at lag 0−2 days.

3.2.1.2.4.   Effect Modification of the PM$_{2.5}$-Mortality Relationship

Multicity epidemiologic studies evaluated in the 2009 PM ISA and 2019 PM ISA provided evidence of city-to-city and regional heterogeneity in PM$_{2.5}$-mortality associations. Within the 2019 PM ISA, studies were evaluated that examined factors that could modify the PM$_{2.5}$-mortality association and potentially explain some of the observed heterogeneity in associations, including season (2019 PM ISA, Section 11.1.6.1), temperature (2019 PM ISA, Section 11.1.6.2), city and regional characteristics (Section 11.1.6.3) such as composition/mixtures (2019 PM ISA, Section 11.1.6.3.1), and exposure factors (i.e., residential infiltration factors and commuting factors) (2019 PM ISA, Section 11.1.6.3.2). Recent multicity studies provide additional insight into some of these factors that could modify the PM$_{2.5}$-mortality association.

The 2009 PM ISA reported some evidence that PM$_{2.5}$-mortality associations are larger in magnitude during the warm season, specifically the spring, with the majority of this evidence coming from U.S. multicity studies (Zanobetti and Schwartz, 2009; Franklin et al., 2008). As discussed in Section 11.1.6.1 of the 2019 PM ISA, across recent multicity studies, there was general agreement that PM$_{2.5}$-mortality associations were larger in magnitude during warmer months. However, it remained unclear whether copollutants confound the seasonal patterns in the associations observed. Across most studies, the pattern of seasonal associations persisted using different methods to examine whether there was evidence of seasonal differences in associations, with some studies relying on stratified analyses (Dai et al., 2014; Samoli et al., 2013) and others incorporating interaction terms between PM$_{2.5}$ and season (Pascal et al., 2014; Lippmann et al., 2013b). The recent studies conducted by Shin et al. (2021a) and Shin et al. (2021b) further inform seasonal analyses, but do not address the uncertainties identified in the 2019

PM ISA. Both studies assessed associations by season through stratified analyses in which the warm season is defined as April−September and the cold season as October−March. In Shin et al. (2021a), when focusing on lag 0, which had the largest magnitude of an association in all-year analyses, there is a clear pattern of the warm season driving the overall association; however, the reverse pattern is reported when focusing on lag 1, complicating the overall interpretation of results from this study. However, in Shin et al. (2021b), which focused on respiratory mortality a slight larger association, with wide confidence intervals, is reported for the warm season (1.0% [95% CI: −1.6, 3.5]) compared with the cold season (0.6% [95% CI: −2.2, 4.1]) at lag 1, the main lag examined for $PM_{2.5}$ and mortality within the study. Across these recent studies there continues to be some evidence indicating larger associations during the warm season, but there are inconsistencies across the individual lags examined.

Within the 2019 PM ISA, an assessment of composition and mixtures (2019 PM ISA, Section 11.1.6.3.1) focused on whether differences in the pollutant mixture across cities could explain heterogeneity in the $PM_{2.5}$-mortality association across cities and regions of the U.S. In the process of examining the association between short-term $PM_{2.5}$ exposure and mortality across 24 Canadian cities, Lavigne et al. (2018) did not focus on whether effect modification by other pollutants could explain heterogeneity, but broadly whether oxidant gases, defined as the redox-weighted average of O_3 and NO_2, modify the $PM_{2.5}$-mortality association. The authors examined the role of oxidant gases on the $PM_{2.5}$-mortality relationship because previous studies have shown that oxidant gases can deplete antioxidants in the lung and increase permeability of the lung epithelium, and that oxidant gases may accelerate photochemical aging of $PM_{2.5}$, potentially changing its toxicity (Lavigne et al., 2018). To assess whether there is evidence of effect modification of the $PM_{2.5}$-mortality relationship by oxidant gases, the authors conducted stratified analyses across tertiles of oxidant gases based on the distribution of oxidant gases across all cities. For nonaccidental mortality, in analyses examining both lag 0 and lag 0−2 days for $PM_{2.5}$, there was a consistent pattern of the $PM_{2.5}$-mortality association being larger in magnitude for the third tertile of oxidant gases. However, there is some variability in the $PM_{2.5}$-mortality association depending on the lag structure used to represent oxidant gases, with some evidence indicating that as the exposure for oxidant gases increased in length, there are larger $PM_{2.5}$-mortality associations for both the second and third tertiles (Figure 3-15). The pattern of associations for nonaccidental mortality is similar for cardiovascular mortality, but there is no evidence of effect modification for respiratory mortality.
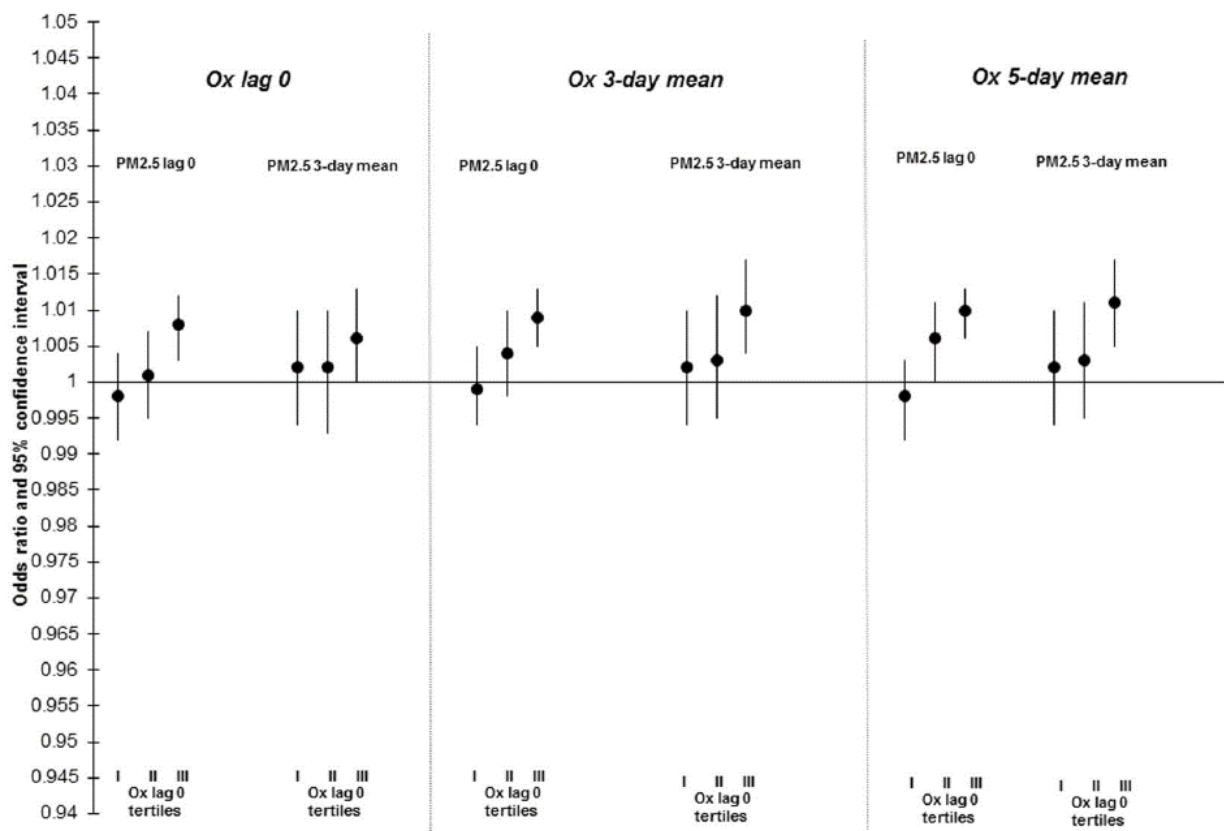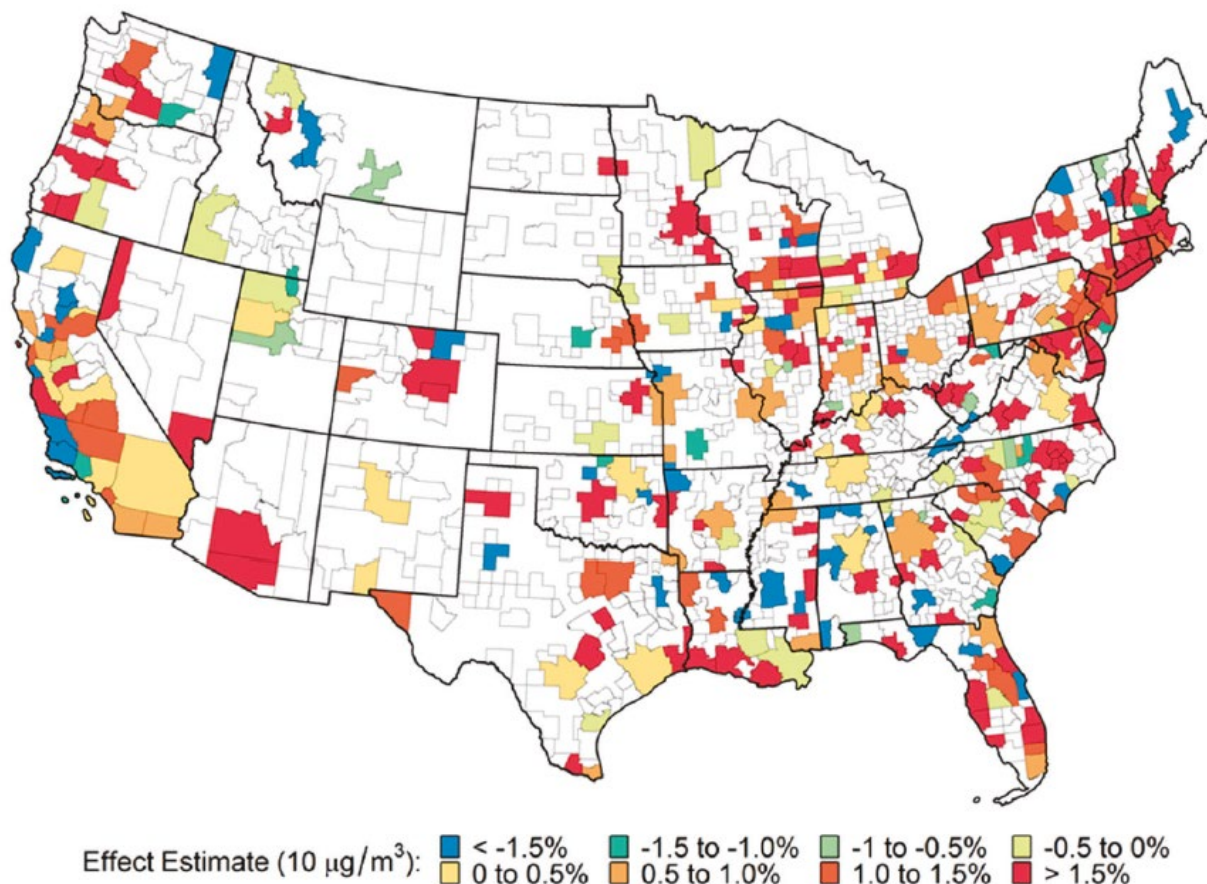
Source: Lavigne et al. (2018)

Figure 3-15   Odds ratio and 95% confidence intervals for lag 0 and lag 0−2 days of nonaccidental mortality across tertiles of lag 0, lag 0−2, and lag 0−4 oxidant gases across 24 Canadian cities.

A recent study by Baxter et al. (2019) expands upon studies evaluated in the 2019 PM ISA (Baxter et al., 2017; Baxter and Sacks, 2014), which provided evidence indicating that combinations of exposure factors representative of residential infiltration (i.e., prevalence of central AC, mean year home was built, and mean size of home) explained some of the heterogeneity in the PM$_{2.5}$-mortality association. As discussed in the 2019 PM ISA (Section 3.4, 2019 PM ISA), examining these exposure factors is important in the context of interpreting health effects associations reported in epidemiologic studies because they can affect the relationship between indoor and outdoor ambient PM concentrations and between personal exposure to ambient PM and ambient PM concentrations.

In a time-series analysis, Baxter et al. (2019) examined the association between short-term PM$_{2.5}$ exposure and nonaccidental mortality in 312 core-based statistical areas (CBSAs) within the U.S. from 1999−2005. In a two-stage analysis, the authors first examined associations with mortality in each CBSA in a time-series analysis and then conducted a meta-regression using a fixed-effects inverse variance weighted linear regression to examine whether individual exposure factors or combinations of exposure factors explained observed heterogeneity. The variables examined within the meta-regression fall within

five categories representative of housing characteristics, commuting, household heating, meteorological factors, and poverty measures. In the first-stage analysis, Baxter et al. (2019) reported a 0.95% (IQR of 2.25)[17] increase in mortality across all CBSAs, but as depicted in Figure 3-16 there is extensive city-to-city variability in associations across the U.S.

Effect Estimate (10 $\mu g/m^3$): ■ < -1.5% ■ -1.5 to -1.0% ■ -1 to -0.5% ■ -0.5 to 0% ■ 0 to 0.5% ■ 0.5 to 1.0% ■ 1.0 to 1.5% ■ > 1.5%

Source: Baxter et al. (2019)

Figure 3-16   Associations between short-term PM2.5 exposure and nonaccidental mortality at lag 1 for the 312 core-based statistical areas examined in Baxter et al. (2019).

In the second-stage analysis, the authors conducted both a univariate and multivariate meta-regression. In the univariate regression, mortality associations larger in magnitude were observed for CBSAs with larger homes, more heating degree days, and a higher percentage of homes heating with oil, while cities with more gas heating had smaller associations. Across all univariate analyses, no

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[17]95% CIs were not presented in this study.

individual factor explained much of the heterogeneity as reflected by $R^2 < 1\%$. For the multivariate model, a backward selection approach was used to develop the final model that included variables for gas heating use, heating degree days, cooling degree days, and variables for home size and age. Compared with the univariate models, the multivariate models explained a larger amount of the heterogeneity in mortality associations across the CBSAs examined, ranging from 11% to 13%. Overall, the results of Baxter et al. (2019) further support studies evaluated in the 2019 PM ISA, which indicated that a combination of factors that influence exposure to $PM_{2.5}$, not an individual factor, explains some of the observed city-to-city and regional heterogeneity reported in multicity epidemiologic studies.

3.2.1.2.5.   Lag Structure of Associations

Within the 2009 PM ISA, the studies evaluated indicated that the effect of short-term $PM_{2.5}$ exposure on mortality was immediate, occurring within the first few days after exposure, with the strongest evidence, in terms of magnitude and precision of the associations, in the range of 0 to 1 day. However, these studies defined the lags to examine a priori, often in accordance with the 1-in-3 or 1-in-6-day sampling schedule of ambient $PM_{2.5}$ monitors. As detailed in Section 11.1.8.1 of the 2019 PM ISA, some studies published since the completion of the 2009 PM ISA conducted more extensive examinations of the lag structure of associations for short-term $PM_{2.5}$ exposures and mortality and continue to support associations being largest in terms of magnitude and precision primarily within the first few days of exposure (i.e., lags of 0 to 1 day) as depicted in Figure 3-14.

Of the recent studies evaluated, Lavigne et al. (2018) and Shin et al. (2021a) in multi-city studies conducted in Canada examined the lag structure of associations primarily through examining single-day lags ranging from 0 to 2 days, with Lavigne et al. (2018) also examining a multi-day lag of 0−1 days. In the single-day lag analyses, Lavigne et al. (2018) and Shin et al. (2021a) both reported positive associations relatively similar in magnitude at lag 0 and 1 with no evidence of an association at lag 2. In the multi-day lag analysis focusing on lag 0−1 day, Lavigne et al. (2018) reported results similar in magnitude to the single-day lag analysis of lag 0 and 1 day. The single-day lag analyses in combination with the multi-day lag analysis conducted by Lavigne et al. (2018) supports the conclusions of previously evaluated studies in the 2009 and 2019 PM ISA that indicated associations largest in magnitude at lags of 0 to 1 day.

3.2.1.2.6.   Examination of the Concentration-Response (C-R) Relationship between Short-Term $PM_{2.5}$ Exposure and Mortality

In the 2009 PM ISA, the examination of the PM-mortality C-R relationship was limited to studies of PM_{10}. Within the multicity studies examined, there was evidence of a linear, no-threshold C-R relationship between short-term PM exposures and mortality with some evidence of differences in the shape of the C-R curve across cities. Studies evaluated in the 2019 PM ISA, focused specifically on

examining the C-R relationship between short-term PM$_{2.5}$ exposure and mortality. Although difficulties remain in assessing the shape of the PM$_{2.5}$-mortality C-R relationship, as identified in the 2009 PM ISA, and studies had not conducted systematic evaluations of alternatives to linearity, the studies evaluated in the 2019 PM ISA continued to provide evidence of a no-threshold linear relationship, with less confidence at concentrations lower than 5 µg/m^3. Additionally, those studies that conducted analyses focused on examining associations at lower PM$_{2.5}$ concentrations provided initial evidence indicating that associations persist and may be larger (i.e., have a steeper slope) at lower PM$_{2.5}$ concentrations.

Liu et al. (2019) in the global analysis examining the association between short-term PM$_{2.5}$ exposure and mortality in 652 cities, also examined country-specific C-R relationships. For each country, a linear term for PM$_{2.5}$ was added to the main model with a B-spline function with knots at the 25th and 75th percentiles of the mean PM$_{2.5}$ concentration across all cities. In C-R analyses consisting of 107 U.S. cities (Figure 3-17a) and 25 Canadian cities (Figure 3-17b), analyses indicated a linear, no-threshold relationship at concentrations often experienced within the U.S. and Canada, with less certainty in the shape of the curve at concentrations less than approximately 8 µg/m^3 and greater than 30 µg/m^3.
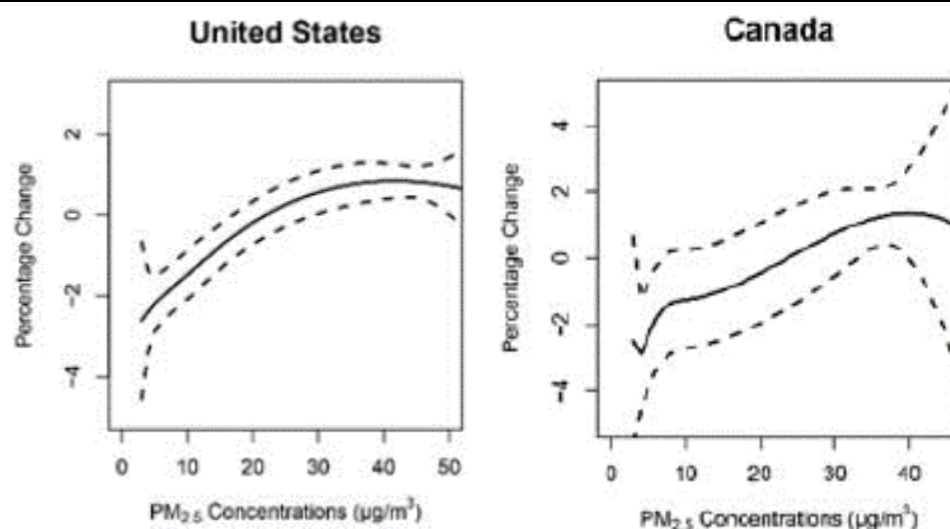
Source: Adapted from Liu et al. (2019)..

Note: As noted in Liu et al. (2019), the "y-axis can be interpreted as the relative change from the mean effect of PM$_{2.5}$ on mortality; the fraction of the curve below zero denotes a smaller estimate compared with the mean effect."

Figure 3-17   Concentration-response curves for the United States (A) and Canada (B) using a B-spline function with knots at the 25th and 75th percentiles of PM$_{2.5}$ concentrations across all cities in each location.

While Liu et al. (2019) focused on nonaccidental mortality, Lavigne et al. (2018) examined the C-R relationship for nonaccidental mortality as well as cardiovascular- and respiratory-related mortality

in an analysis of 24 Canadian cities. The authors used the same model for each mortality outcome, consisting of natural cubic splines with 3 df focusing on 0−2-day $PM_{2.5}$ exposures. Across mortality outcomes examined in Lavigne et al. (2018), C-R curves support a linear relationship at $PM_{2.5}$ concentrations often experienced in the U.S. and Canada, with less certainty in the shape of the curve for nonaccidental mortality at concentrations below approximately 5 $\mu g/m^3$ as reflected by the lower bound of the 95% confidence interval (CI) going below the null and some evidence of nonlinearity in the respiratory mortality C-R relationship as reflected by the inflection point occurring around 7 $\mu g/m^3$ (Figure 3-18). However, compared with nonaccidental mortality, for both cardiovascular and respiratory mortality, the lower bound of the 95% confidence interval was wider and below the null resulting in less confidence in the overall shape of the C-R curve for both mortality outcomes.
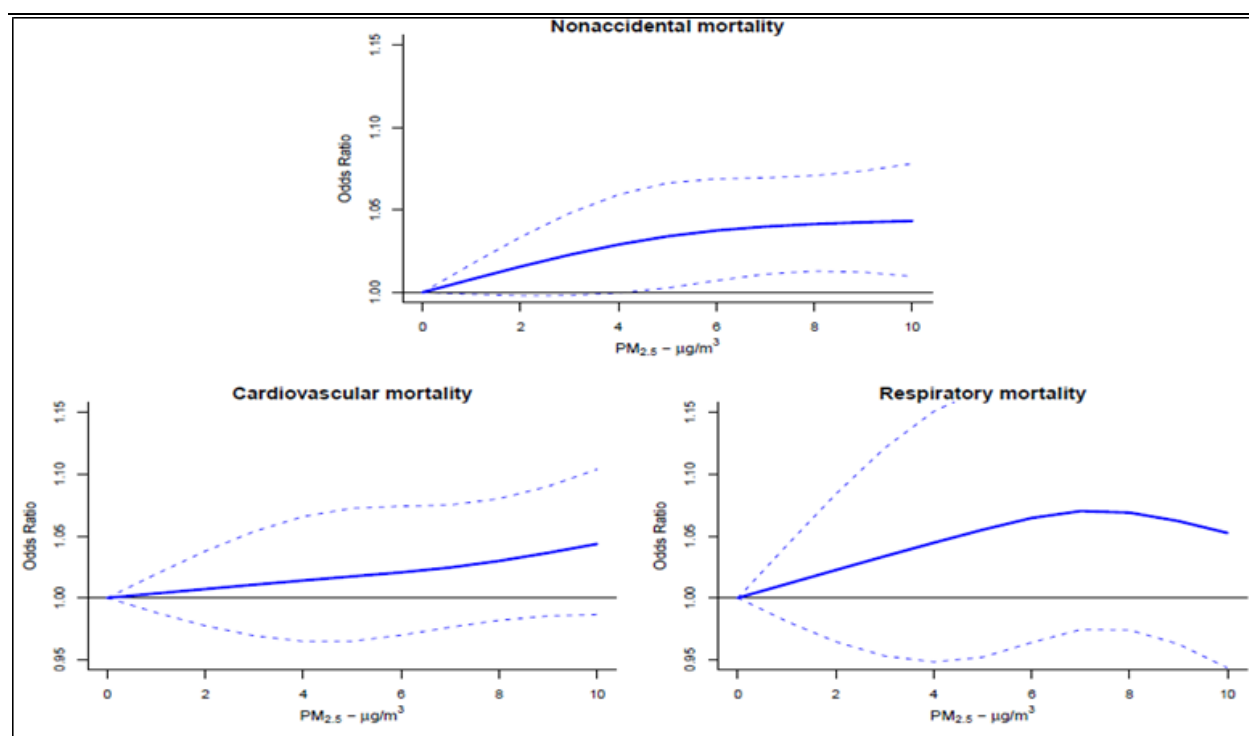
Source: Lavigne et al. (2018)

Figure 3-18   Concentration-response curves for nonaccidental, cardiovascular, and respiratory mortality using natural cubic splines with 3 degrees of freedom for associations with 0−2-day PM2.5 across 24 Canadian cities.

Overall, recent studies, although limited in number continue to provide evidence of a linear, no-threshold relationship between short-term $PM_{2.5}$ exposure and mortality. Additionally, analyses of nonaccidental mortality support previous studies evaluated that indicated confidence in the shape of the C-R relationship down to concentrations in the range of 5−8 $\mu g/m^3$. However, consistent with studies

evaluated in previous assessments, neither study conducted systematic evaluations of alternatives to linearity.

3.2.1.3.   Recent Epidemiologic Studies Examining the $PM_{2.5}$-Mortality Relationship through Accountability Analyses and Alternative Methods for Confounder Control

Within the 2019 PM ISA, in assessing the relationship between short-term $PM_{2.5}$ exposure and mortality several epidemiologic studies were evaluated that employed alternative methods for confounder control (referred to as causal modeling methods in the 2019 PM ISA, Section 11.1.2.1). These studies, which were limited to single-city analyses and used different statistical approaches provided evidence that further confirmed the consistent positive association between short-term $PM_{2.5}$ exposure and mortality reported in numerous multi-city studies and further supported the conclusion of a causal relationship. Since the literature cutoff date of the 2019 PM ISA, additional epidemiologic studies have been identified that implemented alternative methods for confounder control, which further inform the relationship between short-term $PM_{2.5}$ exposure and mortality (Table A-6).

Epidemiologic studies that use alternative methods for confounder control seek to mimic randomized experiments through the use of study design and statistical methods, which reduce the potential bias of effects due to confounding. One such method, generalized propensity score (GPS), estimates the conditional probability of an individual being exposed to the observed ambient concentration, accounting for all measured potential confounders. To assess the associations between short-term $PM_{2.5}$ exposure and mortality, recent studies by Wei et al. (2020) and Wei et al. (2021b) used different GPS approaches.

Wei et al. (2020) evaluated the association between short-term $PM_{2.5}$ exposure and all-cause mortality among Medicare beneficiaries residing in Massachusetts during 2000−2012. In the design stage, to construct the GPS, an ordinary least squares model was used to regress $PM_{2.5}$ against a linear combination of covariates including the copollutants ozone and NO_2 (Wei et al., 2020). In the analysis stage, an ordinary least squares regression was used to fit a linear probability model relating the outcome (death) with the observed exposures and the estimated GPS. Wei et al. (2020) reported 3.04 (95% CI: 2.17, 3.94) excess deaths per 10 million person-days for each 1 μg/m^3 increase in short-term $PM_{2.5}$ exposure. When the analysis was restricted to a range of $PM_{2.5}$ concentrations, the number of excess deaths associated with a 1 μg/m^3 increase in short-term $PM_{2.5}$ exposure increased from 3.33 ($PM_{2.5}$ concentrations < 35 ug/m^3; 95% CI: 2.41, 4.11) to 14.56 ($PM_{2.5}$ concentrations < 5 ug/m^3; 95% CI: 3.96, 24.59), per 10 million person-days.

In a subsequent study, Wei et al. (2021b) used three GPS approaches (linear probability model, weighted least squares, and m-out-of-n random forests [moonRF]), for assessing additive effects of short-term exposures to $PM_{2.5}$ and the copollutants O_3, and NO_2 on mortality rates among Medicare

beneficiaries residing in Massachusetts between 2000 and 2012. To reduce the computational burden of the linear probability model GPS approach, weighted least squares and moonRF GPS approaches were proposed as alternatives. Consistent with Wei et al. (2020), for the linear probability model, the authors had both a design stage and an analysis stage. In the design stage, the GPS for $PM_{2.5}$ concentrations was constructed by fitting a linear regression of the predicted $PM_{2.5}$ concentration against a column vector of covariates. In the analysis stage, a linear probability model was fitted with the outcome of death, against the predicted $PM_{2.5}$ concentration and the GPS.

For the weighted least squares method, there was also a design stage and an analysis stage. In the design stage, the person-days that had the same sex, race, age, Medicaid eligibility, ZIP code of residence, and date were aggregated as a single record and assigned the numbers of person-days for that record as weight. The GPS was constructed by fitting a weighted linear regression of the predicted $PM_{2.5}$ concentration against all the covariates from this aggregated data set, with continuous covariates modeled with cubic polynomials. The average outcome for each aggregated person-day group was calculated and assigned to the person-day in the aggregated data set. A weighted linear regression was then fitted for the averaged outcome against the predicted $PM_{2.5}$ concentration and the estimated GPS.

The moonRF method is based on the random forest method, which is a non-parametric machine learning approach of classification for possible nonlinear relationships and interactions through building individual decision trees through resampling. The m-out-of-n bootstrapping method resamples the m observations out of an original data set $(1,…,n)$ without replacement, where $m << n$ (Wei et al., 2021b). In the design stage, the number of person-days aggregated for each record in the aggregated data set was used as the frequency weight and sampled 62,000 person-days without replacement. With this sample, trees were built for $PM_{2.5}$ to make predictions of the exposure for each person-day in the aggregated data set, which was repeated 100 times. The final predicted $PM_{2.5}$ concentration for each person-day was obtained by averaging the predictions of the 100 trees. The GPS was constructed by using the averaged predictions of the 100 trees as the predicted $PM_{2.5}$ concentration and covariates for each person-day in the aggregated data set. In the analysis stage, the authors fit a weighted regression of the averaged outcome against the predicted $PM_{2.5}$ concentration and the estimated GPS using the aggregated data set to obtain the estimate for the additive effect of short-term $PM_{2.5}$ exposure on mortality rate.

Wei et al. (2021b) reported that the linear probability model and the weighted least squares model produced identical results with the estimated annual number of early deaths associated with a 1 $\mu g/m^3$ increase in 24-hour avg $PM_{2.5}$ concentrations being 92 (95% CI: 67, 117). However, the moonRF approach estimated a smaller number of annual deaths 69 (95% CI: 44, 95). When restricting the analysis to person-days with 24-hour average $PM_{2.5}$ concentrations below < 35 $\mu g/m^3$, the authors estimated a larger annual number of early deaths for each method (101 [95% CI: 74, 127] for the linear probability model and weighted least squares approaches and 78 [95% CI: 52, 105] for the moonRF approach).

In another recent study that employed alternative methods for confounder control, using data from the National Center for Health Statistics in 135 U.S. cities, Schwartz et al. (2018a) utilized three

statistical methods: instrumental variable analysis, a negative exposure control, and marginal structural models to estimate the association between local pollution, including $PM_{2.5}$, and daily deaths. Instrumental variable analysis constructs a single or set of instrument variables that represent variations in the exposure that are randomized with respect to both measured and unmeasured confounders. The instrument variables considered were planetary boundary layer, wind speed, and sea level pressure. Negative exposure control identifies a negative exposure variable, which is likely to be correlated with unmeasured potential confounders but could not be a cause of the outcome of interest. Negative exposure controls serve as instruments for the unmeasured confounders. If such confounders exist, control for the negative exposure would be expected to reduce or eliminate the estimated effect of the exposure of interest. If no such confounders exist, then control for the negative exposure would be expected to have no change in the association between the exposure and outcome, which indicates no confounding by any measured or unmeasured variables. Marginal structural models estimate the marginal effects of exposure by using inverse probability weights of time-varying exposures to render the exposure independent of the measured covariates. If the exposure is independent of covariates, its effect on the outcome cannot be confounded by them and resulting estimates do not depend on the distributions of confounders. The instrumental variable approach estimated that mortality increased by 1.54% (95% CI: 1.12, 1.97) at lag 0−1 for a 10 μg/m^3 increase in 24-hour avg $PM_{2.5}$ concentrations. When restricted to days with 24-hour average $PM_{2.5}$ concentrations below 25 μg/m^3, the instrument for $PM_{2.5}$ was associated with an increase of 1.70% (95% CI: 1.11, 2.29). With the negative control exposure method, there was −0:1% (95% CI: −0.5, 0.3) change in mortality. For the marginal structural models, there was an estimated 0.75% (95% CI: 0.35, 1.15) increase in mortality. When restricted to days with 24-hour average $PM_{2.5}$ concentrations below 25 μg/m^3, the marginal structural model also reported a 0.83% (95% CI: 0.39, 1.27) increase in mortality, albeit smaller in magnitude than the instrumental variable approach. Overall, the results of Schwartz et al. (2018a) continue to support a relationship between short-term $PM_{2.5}$ exposure and mortality.

Recent epidemiologic studies that employed alternative methods for confounder control to examine the association between short-term $PM_{2.5}$ exposure and mortality reported consistent positive associations within large cohorts across multiple cities in the U.S. Furthermore, the use of alternative methods for confounder control within these studies aims to reduce the uncertainties related to potential confounders that may bias reported associations. Overall, these recent studies further support the conclusions of the 2019 PM ISA with respect to short-term $PM_{2.5}$ exposure and mortality.

3.2.1.4.   Summary of Recent Evidence in the Context of the 2019 Integrated Science Assessment for Particulate Matter Causality Determination for Short-Term PM$_{2.5}$ Exposure and Mortality

The few multicity epidemiologic studies conducted since the literature cutoff date of the 2019 PM ISA, provide additional support to the evidence base that contributed to the conclusion of a *causal relationship* between short-term $PM_{2.5}$ exposure and mortality. Recent U.S. and Canadian studies in

combination with previously evaluated multicity studies provide evidence of consistent positive associations with all-cause and nonaccidental mortality, primarily within the first few days after exposure (i.e., lag 0 and 1 day), across studies conducted in different geographic locations and in populations with different demographic characteristics. Additionally, these positive associations persist across studies that used different statistical models, exposure assessment approaches, and methods for confounder control. Overall, recent studies continue to support a relationship between short-term $PM_{2.5}$ exposure and mortality at lower mean 24-hour average concentrations, generally below 12 µg/m³, as detailed in the 2019 PM ISA.

The limited assessment of cause-specific mortality in recent studies provides similar results to previously evaluated studies demonstrating a consistent relationship with cardiovascular mortality and more variability in the magnitude and precision of associations with respiratory mortality. Consistent with studies evaluated in the 2019 PM ISA, recent studies indicate that associations between short-term $PM_{2.5}$ exposure and mortality are relatively unchanged in copollutant models but may be larger in magnitude in the presence of some co-occurring pollutants (i.e., oxidant gases). In addition, factors that have been shown to vary between cities and regions of the U.S., such as housing characteristics, have been shown to explain some of the city-to-city and regional variability observed in $PM_{2.5}$-mortality associations in multi-city epidemiologic studies. The continued assessment of the C-R relationship between short-term $PM_{2.5}$ exposure and mortality further supports a linear, no-threshold relationship, with less confidence in the shape at concentrations below 5 µg/m³. Additionally, recent studies that employed alternative methods for confounder control provide additional support for a relationship between short-term $PM_{2.5}$ exposure and mortality.

3.2.2.   Long-Term PM₂.₅ Exposure

The following sections represent a summary of the evidence and the corresponding causality determination for long-term $PM_{2.5}$ exposure and mortality presented within the 2019 PM ISA (Section 3.2.2.1) along with an evaluation of recent epidemiologic studies that fall within the scope of the Supplement (i.e., studies conducted in the U.S. and Canada) and were published since the literature cutoff date of the 2019 PM ISA (Section 3.2.2.2). [18] In addition, with the expansion of in epidemiologic studies that used statistical approaches that attempt to more extensively account for confounders and are more robust to model misspecification (i.e., used alternative methods for confounder control), recent studies that employed such methods are also evaluated (Section 3.2.2.3), which can further inform the relationship between long-term $PM_{2.5}$ exposure and mortality. Finally, a summary of the results of recent studies evaluated within the section is presented in the context of the scientific conclusions detailed in the 2019 PM ISA (Section 3.2.2.4). The evaluation of recent studies on long-term $PM_{2.5}$ exposure and

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[18] Throughout this section, as detailed in the Preface of the 2019 PM ISA (Section P.3.2.2), risk estimates from epidemiologic studies examining long-term exposures are for a 5 µg/m³ increase in annual concentrations, unless otherwise noted.

mortality presented in this Supplement adds to the collective body of evidence reviewed in the process of reconsidering the PM NAAQS.

3.2.2.1.   Summary and Causality Determination from 2019 Integrated Science Assessment for Particulate Matter

Cohort studies evaluated in the 2019 PM ISA provided consistent evidence of positive associations between long-term $PM_{2.5}$ exposures and total (nonaccidental) mortality from studies conducted mainly in North America and Europe. Many analyses further evaluated the association between long-term $PM_{2.5}$ exposures and the risk of mortality based on the original American Cancer Society (ACS) study ([Pope et al., 1995](#)), added new details about deaths due to cardiovascular disease (including IHD) and respiratory disease (including COPD), and extended the follow-up period of the ACS to 22 years (1982−2004). Adding to this evidence, U.S. and Canadian cohort studies demonstrated consistent, positive associations between long-term $PM_{2.5}$ exposure and mortality across various spatial extents, exposure assessment metrics, and statistical techniques, and locations, where mean annual average concentrations are ≤ 12 µg/m^3 (2019 PM ISA, Section 11.2.2.2). Additionally, the evidence from these studies reduced uncertainties related to potential copollutant confounding (2019 PM ISA, Section 11.2.3) and continued to provide strong support for a linear, no-threshold C-R relationship (2019 PM ISA, Section 11.2.4). The body of evidence for total mortality was supported by generally consistent, positive associations with cardiovascular and respiratory mortality.

In addition to evaluating epidemiologic studies that examined the relationship between long-term $PM_{2.5}$ exposure and mortality, the 2019 PM ISA characterized whether evidence supported biologically plausible mechanisms by which long-term $PM_{2.5}$ exposure could lead to mortality (2019 PM ISA, Section 11.2.1). This evaluation consisted of an assessment of animal toxicological, controlled human exposure, and epidemiologic studies of morbidity effects that are the largest contributors to total (nonaccidental) mortality, specifically, cardiovascular and respiratory morbidity and metabolic disease (2019 PM ISA, Section 6.2.1, Section 5.2.1, and Section 7.2.1, respectively). Plausible mechanisms were identified by which inhalation exposure to $PM_{2.5}$ could progress from initial events to endpoints relevant to the cardiovascular system and to population outcomes such as IHD, stroke and atherosclerosis (2019 PM ISA, Section 6.2.1). Similarly, available evidence was characterized by which inhalation exposure to $PM_{2.5}$ could progress from initial events to endpoints relevant to the respiratory system and to population outcomes such as exacerbation of COPD (2019 PM ISA, Section 5.2.1). In addition, there was evidence for plausible mechanisms by which inhalation exposure to $PM_{2.5}$ could progress from initial events (e.g., pulmonary inflammation, autonomic nervous system activation) to intermediate endpoints (e.g., insulin resistance, increased blood glucose and lipids) and result in population outcomes such as metabolic disease and diabetes. In summary, there was coherence of effects across the scientific disciplines (i.e., animal toxicological, controlled human exposure, and epidemiologic studies) and biological plausibility for $PM_{2.5}$-related cardiovascular (2019 PM ISA, Chapter 6), respiratory (2019 PM

ISA, Chapter 5), and metabolic (2019 PM ISA, Chapter 7) disease, which supports the $PM_{2.5}$-mortality relationship.

This section describes the evaluation of evidence included in the 2019 PM ISA for total (nonaccidental) mortality, with respect to the causality determination for long-term exposures to $PM_{2.5}$ using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015). The key evidence, as it relates to the causal framework, is summarized in Table 3-5.

Table 3-5   Summary of evidence for a *causal relationship* between long-term PM$_{2.5}$ exposure and total mortality from the 2019 Integrated Science Assessment for Particulate Matter.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References and Sections in the 2019 PM ISA[b]	PM$_{2.5}$ Concentrations Associated with Effects ($\mu g/m^3$)[c]
Consistent epidemiologic evidence from multiple, high-quality studies at relevant PM$_{2.5}$ concentrations	Positive associations between long-term PM$_{2.5}$ exposure and mortality in the multiple analyses of the ACS and HSC cohorts, with effect estimates similar in magnitude, even after adjustment for common potential confounders.	Section 11.2.2.1	Mean across studies: 11.4−23.6
	Positive associations between long-term PM$_{2.5}$ exposure and mortality in the multiple analyses of the Medicare cohort, with effect estimates similar in magnitude, even after adjustment for common potential confounders.	Section 11.2.2.2	Mean across studies: 8.12−12.0
	Positive associations between long-term PM$_{2.5}$ exposure and mortality in the multiple analyses of Canadian cohorts, with effect estimates similar in magnitude, even after adjustment for common potential confounders.	Section 11.2.2.2	Mean across studies: 8.7−9.1
	Positive associations between long-term PM$_{2.5}$ exposure and mortality in the multiple North American occupational cohorts, even after adjustment for common potential confounders.	Section 11.2.2.2	Mean across studies: 12.7−17.0
	Positive associations with cardiovascular, respiratory, and lung cancer mortality.	Section 6.3.10.1	Mean across studies: 4.1−17.9
		Section 5.2.10	Mean across studies: 4.1−17.9
		Section 10.2.5.1	Mean across studies: 6.1−33.7
Epidemiologic evidence from copollutant models provides some support for an independent PM$_{2.5}$ association	Positive associations observed between long-term PM$_{2.5}$ exposure and total mortality remain relatively unchanged after adjustment for O$_3$, NO$_2$, and PM$_{10-2.5}$. When reported, correlations with copollutants were highly variable (low to high).	Section 11.2.3; Figure 11-20; Figure 11-21	

Table 3-5 (Continued): Summary of evidence for a *causal relationship* between long-term PM$_{2.5}$ exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References and Sections in the 2019 PM ISA[b]	PM$_{2.5}$ Concentrations Associated with Effects (µg/m^3)[c]
Consistent positive epidemiologic evidence for associations between PM$_{2.5}$ exposure and total mortality across exposure measurement metrics	Positive associations consistently observed across studies that used fixed-site (i.e., monitors), model (e.g., CMAQ, dispersion models), and satellite-based (e.g., AOD observations from satellites) methods, including hybrid methods that combine two or more of these methods.	Section 11.2.2.5; Jerrett et al. (2016)	
Epidemiologic evidence supports a linear, no-threshold C-R relationship	No evidence for deviation from linearity in several U.S. and Canadian cohorts.	Section 11.2.2.3	
Biological plausibility from studies of cardiovascular and respiratory morbidity and lung cancer incidence and mortality	Cardiovascular morbidity studies provide expanded body of evidence for associations between long-term PM$_{2.5}$ exposure and CHD, stroke, and atherosclerosis, providing biological plausibility for a relationship between long-term PM$_{2.5}$ exposure and cardiovascular mortality.	Section 6.3 Miller et al. (2007) Chi et al. (2016)	Mean across studies: 10.7−13.4
	Respiratory morbidity studies provide some evidence for an association between long-term PM$_{2.5}$ exposure and development of COPD, providing limited biological plausibility for a relationship between long-term PM$_{2.5}$ exposure and respiratory mortality.	Section 5.2.5	
	Consistent epidemiologic evidence for associations between PM$_{2.5}$ exposure and lung cancer incidence and mortality in cohort studies conducted in the U.S., Canada, Europe, and Asia.	Section 10.2.5.1 Figure 10-3	Mean across U.S. and Canadian studies: 6.3−23.6

Note: This table corresponds to Table 11-8 in the 2019 PM ISA.

ACS = American Cancer Society; AOD = aerosol optical depth; CHD = coronary heart disease; CMAQ = Community Multiscale Air Quality; COPD = chronic obstructive pulmonary disease; C-R = concentration-response; HSC = Harvard Six Cities; µg/m^3 = microgram per cubic meter; NO$_2$ = nitrogen dioxide; O$_3$ = ozone; PM$_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 µm; PM$_{10-2.5}$ = particulate matter with a nominal mean aerodynamic diameter greater than 2.5 µm and less than or equal to 10 µm.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to the causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described in the 2019 PM ISA.

[c]Describes the PM$_{2.5}$ concentrations with which the evidence is substantiated.

The strongest evidence supporting the conclusion of a *causal relationship* between long-term $PM_{2.5}$ exposure and total mortality in the 2009 PM ISA was derived from analyses of the ACS and Harvard Six Cities (HSC) cohorts. Extended analyses and reanalysis of these cohorts included in the 2019 PM ISA continued to support this relationship, demonstrating consistent positive associations for total (nonaccidental mortality) and across different cause-specific mortality outcomes. A series of analyses of the Medicare cohort of U.S. individuals provided additional support, culminating with the largest cohort study of nearly 61 million U.S. Medicare enrollees that reported positive associations with increases in $PM_{2.5}$ concentrations and stronger associations in areas where the mean annual $PM_{2.5}$ concentrations were ≤ 12 µg/m^3 (Di et al., 2017b). Another series of studies conducted in Canada provided results consistent with those of the Medicare cohort (i.e., positive associations between long-term $PM_{2.5}$ exposure and total mortality in areas where mean annual $PM_{2.5}$ concentrations are ≤ 12 µg/m^3). One difference between these studies was that the Canadian cohorts include all adults (age 25+ years) and the Medicare cohort only included adults age 65+ years, demonstrating that these effects are not specific to one lifestage, but affect all adults. Also, an additional line of evidence was available that includes results from a number of cohorts that recruited subjects based on their place of employment, including female nurses, female teachers, male health professionals, and male truck drivers, which show consistent, positive associations between long-term $PM_{2.5}$ exposure and total mortality.

Evidence included in the 2019 PM ISA helped to reduce uncertainties related to potential copollutant confounding of the relationship between long-term $PM_{2.5}$ exposure and mortality. Multiple studies evaluated ozone (2019 PM ISA, Figure 11-20) and NO_2 (2019 PM ISA, Figure 11-21) in copollutant models and observed similar hazard ratios for $PM_{2.5}$ regardless of whether ozone or NO_2 were included in the model. This supports an independent effect of long-term $PM_{2.5}$ exposure on mortality. Evidence for other potential copollutants (e.g., SO_2, CO) was limited.

Studies evaluated in the 2019 PM ISA used a variety of both fixed-site (i.e., monitors), model (e.g., CMAQ, dispersion models), and satellite-based (e.g., AOD measurements from satellites) methods, including hybrid methods that combine two or more fixed-site, model, and/or satellite-based techniques to measure, estimate, or predict $PM_{2.5}$ concentrations for use in assigning long-term $PM_{2.5}$ exposure in epidemiologic studies. Overall, the exposure assessment technique had little influence on study results, with consistently positive associations of similar magnitude observed across studies using a variety of exposure assessment techniques. Notably, Jerrett et al. (2016) applied fixed-site measurements and satellite-based observations of AOD to a common data set, the ACS cohort, and calculated effect estimates for circulatory and IHD mortality associated with $PM_{2.5}$ using both methods. They observed consistently positive associations between long-term $PM_{2.5}$ exposure and mortality, regardless of the exposure assessment technique used to assign exposure. Additionally, Jerrett et al. (2016) combined multiple exposure assessment techniques into an ensemble model, weighted by model fit, and continued to observe similar positive associations with mortality. These results support an independent effect of

long-term $PM_{2.5}$ exposure on mortality that is not overtly influenced by or is a residual of the exposure assessment technique used in the study.

The number of studies that examined the shape of the C-R function for long-term $PM_{2.5}$ exposure and mortality substantially increased between the 2009 PM ISA and the 2019 PM ISA. These studies used a number of different statistical techniques to evaluate the shape of the C-R function, including natural cubic splines, restricted cubic splines, penalized splines, thin-plate splines, and cutpoint analyses (2019 PM ISA, Table 11-7), and generally observed linear, no-threshold relationships down to 4−8 µg/m³. Few studies have conducted extensive analyses exploring alternatives to linearity when examining the shape of the $PM_{2.5}$-mortality C-R relationship. Among these studies, there was some emerging evidence for a supralinear C-R function, with steeper slopes observed at lower $PM_{2.5}$ concentrations. Although few, such supralinear C-R functions were most commonly observed for cardiovascular mortality compared with total (nonaccidental) or respiratory mortality.

The 2009 PM ISA concluded that there is not sufficient evidence to differentiate the components or sources more closely related to health outcomes when compared with $PM_{2.5}$ mass, although the evidence for long-term exposure and mortality was limited. Several studies included in the 2019 PM ISA examined the relationship between long-term exposure to PM components and mortality (2019 PM ISA, Figure 11-24). Collectively, these studies continued to demonstrate that no individual $PM_{2.5}$ component or source was a better predictor of mortality than $PM_{2.5}$ mass.

Overall, epidemiologic studies examined in the 2019 PM ISA built upon and further reaffirmed the conclusions of the 2009 PM ISA for total mortality. The evidence, particularly from the assessment of $PM_{2.5}$-related cardiovascular and metabolic diseases, with more limited evidence from respiratory morbidity, provided biological plausibility for mortality due to long-term $PM_{2.5}$ exposures. In conclusion, the consistent positive associations observed across cohort studies conducted in various locations across North America were further supported by the results from copollutant analyses indicating robust associations independent of O_3 and NO_2. **Collectively, this body of evidence was sufficient to conclude that a causal relationship exists between long-term $PM_{2.5}$ exposure and total mortality.**

3.2.2.2.   Recent U.S. and Canadian Cohort Studies

Recent cohort studies conducted in the U.S. and Canada build upon the strong evidence base evaluated in the 2019 PM ISA, as well as previous in assessments, which provided the scientific rationale supporting a *causal relationship* between long-term $PM_{2.5}$ exposure and mortality (Section 3.2.2.1). In addition to examining the relationship between long-term $PM_{2.5}$ exposure and all-cause or nonaccidental mortality (Section 3.2.2.2.1) and cause-specific mortality (Section 3.2.2.2.2), some studies also further examined issues relevant to expanding the overall understanding of the effect of long-term $PM_{2.5}$ exposure on mortality. Specifically, recent studies have assessed the effect of long-term $PM_{2.5}$ exposure on mortality in populations with underlying health conditions (Section 3.2.2.2.3), examined the role of